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(54) Title: THERAPEUTIC METHODS USING SMADS
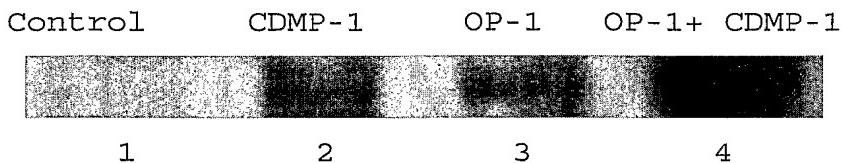
(57) Abstract: Methods of inducing the expression of a Smad in a cell or tissue comprising the step of contacting the cell or tissue capable of expressing the Smad with a bone morphogenic protein are provided. Methods of inducing tissue formation and repairing a tissue defect or regenerating tissue, at a target locus in a mammal comprising the step of administering to the target locus a Smad are also provided.

Therapeutic Methods Using Smads

Technical Field of the Invention

[0001]   The present invention relates to methods for tissue formation, repair and regeneration using Smads.

5   Background of the Invention

[0002]   The TGF-ß superfamily represents a large number of evolutionarily conserved proteins with diverse activities involved in growth, differentiation, cell migration, development, apoptosis and tissue
10   morphogenesis and repair. This large family includes the bone morphogenic proteins (BMPs), TGF-ßs and activins. Each subgroup of proteins initiates a unique signaling cascade activated by the formation of a complex with a receptor. The receptors for this family
15   of proteins are type I also known as activin receptor-like kinases (ALKs) and type II serine/threonine kinases. Several such receptors have been identified thus far. The type II receptors are constitutively active. Upon ligand binding the type II receptor
20   phosphorylates particular serine and threonine residues in the type I receptor. The type I serine/threonine

kinases become activated and transduce signals to downstream molecules.

[0003]   The downstream molecules in the signaling cascade include the Smads. These molecules are vertebrate counterparts to the *Drosophila* and *Caenorhabditis elegans*, proteins known as Mad (*mothers against dpp)* and Sma, respectively. The name Smad originates from a fusion between Mad and Sma. In recent years, several Smads have been identified (Smad 1-8) (Derynck R. et al., 1996, "Nomenclature: Vertebrate mediators of TGF-ß family signals", Cell, 18, 173). The Smads can be divided into three groups: receptor-regulated Smads (R-Smads), common-partner Smads (Co-Smads) and inhibitory Smads (I-Smads). R-Smads are bound to the cell membrane through membrane bound proteins. They transiently interact with and are activated by phosphorylation by activated type I receptor kinases. R-Smads include Smad1, Smad2, Smad3, Smad5 and Smad8. Of those, Smad2 and Smad3 are TGF-β- and activin-specific, whereas Smad1, Smad5 and Smad8 are BMP-specific. The activated R-Smads recruit Co-Smads and these heteromeric complexes translocate to the nucleus. Co-Smads include Smad4. These nuclear Smad complexes bind to DNA directly or indirectly through other DNA-binding proteins, and regulate the transcription of target genes. I-Smads interact with the activated type I receptor, and prevent R-Smads from interacting with activated type I receptors. I-Smads include Smad6 and Smad7.

[0004]   As described above, the TGF-ß superfamily of proteins have important roles in various physiological events including the inductive properties of the proteins belonging to the BMP family. Therefore, there

remains a need for identifying means useful for
promoting tissue regeneration in patients with traumas
caused, for example, by injuries or degenerative
disorders.

[0005]   The ability to induce Smad protein expression
in sufficient quantities at a target locus would be very
useful in orthopedic medicine, certain types of plastic
surgery, dental and various periodontal and craniofacial
reconstructive procedures, and procedures generally
involving bone, cartilage, tendon, ligament and neural
regeneration. Several Smad genes are now cloned and may
be recombinantly expressed in a variety of host systems.
The ability to recombinantly produce active Smads,
including variants and fragments thereof, and to express
them at a target locus makes potential therapeutic
treatments using these proteins either alone or together
with BMPs feasible.

Summary of the Invention

[0006]   This invention is based on the discovery that
Smad expression is induced in the presence of various
bone morphogenic proteins such as OP-1 (BMP-7) and
CDMPs. Therefore, this invention provides a method of
inducing the expression of a Smad in a cell or tissue
comprising the step of contacting the cell or tissue
capable of expressing a Smad with a bone morphogenic
protein (BMP). In some embodiments, the tissue is
selected from the group consisting of bone, cartilage,
tendon, ligament and neural tissue. In one preferred
embodiment, the tissue is bone or cartilage. In another
preferred embodiment, the tissue is tendon or ligament.
In a more preferred embodiment, the tissue is bone. In

another more preferred embodiment, the tissue is
cartilage.

[0007]   In some embodiments, the cells used in the
methods of this invention are progenitor cells. In some
embodiments, the progenitor cells include an
osteoprogenitor cell, a cartilage progenitor cell, a
ligament progenitor cell, a tendon progenitor cell, or a
neural progenitor cell. In a preferred embodiment, the
progenitor cell is an osteoprogenitor cell or a
cartilage progenitor cell. In another preferred
embodiment, the progenitor cell is a tendon progenitor
cell or a ligament progenitor cell. In a more preferred
embodiment, the progenitor cell is an osteoprogenitor
cell. In another more preferred embodiment, the
progenitor cell is a cartilage progenitor cell.

[0008]   In some embodiments, the cell or tissue is
contacted with more than one BMP. In some embodiments,
the cell or tissue is contacted with two BMPs. BMPs
include, but are not limited to, OP-1 (BMP-7), OP-2, OP-
3, COP-1, COP-3, COP-4, COP-5, COP-7, COP-16, BMP-2,
BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, BMP-9, BMP-10, BMP-
11, CDMP-3 (BMP-12), CDMP-2 (BMP-13), CDMP-1 (BMP-14),
BMP-15, BMP-16, BMP-17, BMP-18, GDF-1, GDF-2, GDF-3,
GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11, GDF-
12, MP121, dorsalin-1, DPP, Vg-1, Vgr-1, 60A protein,
NODAL, UNIVIN, SCREW, ADMP, and NEURAL. In one
preferred embodiment, the BMP is OP-1 (BMP-7). In
another preferred embodiment, the BMP is CDMP-1 or GDF-
5. In yet another preferred embodiment, the first bone
morphogenic protein is OP-1 and the second bone
morphogenic protein is CDMP-1 or GDF-5.

[0009]   In some embodiments, the Smads used in the
methods of the present invention include Smad1, Smad2,

Smad3, Smad5 and Smad8. In a preferred embodiment, the Smad is Smad5. In another preferred embodiment, the Smad is a recombinant Smad.

[0010] In some embodiments, the cell or tissue used in the method of inducing the expression of a Smad in a cell or tissue is further capable of expressing a serine/threonine kinase receptor. In some embodiments the serine/threonine kinase receptor is selected from the group consisting of type I and type II receptors. In some embodiments, only type I receptors are used. In some embodiments, only type II receptors are used. In some embodiments, both type I and type II receptors are used. Preferably, the type I and type II receptors are recombinant. In some embodiments the serine/threonine kinase receptors are linked to an expression control sequence. In some embodiments, the expression control sequence comprises a constitutive promoter. In some embodiments, the expression control sequence comprises an inducible promoter. In some embodiments, the type I receptor is an activin receptor-like kinase (ALK). ALKs include but are not limited to ALK-1, ALK-2, ALK-3, ALK-4, ALK-5, ALK-6, ALK-7 and fragments thereof.

[0011] The invention also provides gene therapy methods of inducing tissue formation, repairing a tissue defect or regenerating tissue at a target locus. In some embodiments, the invention provides a method of inducing tissue formation at a target locus in a mammal comprising the step of administering to the target locus a nucleic acid encoding a Smad. In some embodiments, the invention provides a method of inducing tissue formation at a target locus in a mammal comprising the step of administering to the target locus a vector comprising a nucleic acid encoding a Smad operably

linked to an expression control sequence. In some
embodiments, the invention provides a method of inducing
tissue formation at a target locus in a mammal
comprising the step of administering to the target locus
a cell comprising a vector comprising a nucleic acid
encoding a Smad operably linked to an expression control
sequence.

[0012] The invention further provides a method of
repairing a tissue defect or regenerating tissue at a
target locus in a mammal comprising the step of
administering to the target locus a nucleic acid
encoding a Smad. In some embodiments, the invention
provides a method of repairing a tissue defect or
regenerating tissue at a target locus in a mammal
comprising the step of administering to the target locus
a vector comprising a nucleic acid encoding a Smad
operably linked to an expression control sequence. In
some embodiments, the invention provides a method of
repairing a tissue defect or regenerating tissue at a
target locus in a mammal comprising the step of
administering to the target locus a cell comprising a
vector comprising a nucleic acid encoding a Smad
operably linked to an expression control sequence.

[0013] In some embodiments, the tissue in the gene
therapy methods of the present invention is selected
from the group consisting of bone, cartilage, tendon,
ligament and neural tissue. In one preferred
embodiment, the tissue is bone or cartilage. In another
preferred embodiment, the tissue is tendon or ligament.
In a more preferred embodiment, the tissue is bone. In
another more preferred embodiment, the tissue is
cartilage.

[0014]   In some embodiments, the cells used in the gene therapy methods of this invention are progenitor cells. In some embodiments, the progenitor cells include an osteoprogenitor cell, a cartilage progenitor cell, a ligament progenitor cell, a tendon progenitor cell, or a neural progenitor cell. In a preferred embodiment, the progenitor cell is an osteoprogenitor cell or a cartilage progenitor cell. In another preferred embodiment, the progenitor cell is a tendon progenitor cell or a ligament progenitor cell. In a more preferred embodiment, the progenitor cell is an osteoprogenitor cell. In another more preferred embodiment, the progenitor cell is a cartilage progenitor cell.

[0015]   In some embodiments, the expression control sequence operably linked to the nucleic acid encoding a Smad comprises a constitutive promoter. In other embodiments, the expression control sequence operably linked to the nucleic acid encoding a Smad comprises an inducible promoter. A Smad according to this invention includes, but is not limited to, Smad1, Smad2, Smad3, Smad5, Smad8 and fragments thereof. In a preferred embodiment, the Smad is Smad5. In another preferred embodiment, the Smad is a recombinant Smad.

[0016]   In some embodiments, the methods of inducing tissue formation, repairing a tissue defect or regeneration tissue of this invention further comprise the step of administering to the target locus a serine/threonine kinase receptor. In some embodiments, a nucleic acid encoding a serine/threonine kinase receptor is administered. In some embodiments, a vector comprising a nucleic acid encoding a serine/threonine kinase receptor operably linked to an expression control

sequence is administered. In other embodiments, a cell comprising a vector comprising a nucleic acid encoding a serine/threonine kinase receptor operably linked to an expression control sequence is administered.

[0017]   In some embodiments, the expression control sequence operably linked to the a serine/threonine kinase receptor comprises a constitutive promoter. In some embodiments, the expression control sequence operably linked to the serine/threonine kinase receptor comprises an inducible promoter.

[0018]   In some embodiments, the serine/threonine kinase receptor used in the gene therapy methods of inducing tissue formation, repairing a tissue defect or regenerating tissue at a target locus, is selected from the group consisting of type I and type II receptors. In some embodiments, only type I receptors are used. In some embodiments, only type II receptors are used. In some embodiments both type I and type II receptors are used. Preferably recombinant type I and recombinant type II receptors are used. In some embodiments, the type I receptor is an activin receptor-like kinase (ALK). The ALKs that may be used in the present invention include, but are not limited to ALK-1, ALK-2, ALK-3, ALK-4, ALK-5, ALK-6, ALK-7, and fragments thereof. In a preferred embodiment, the ALK is ALK-2, ALK-3, ALK-6 and fragments thereof.

[0019]   In some embodiments, the methods of inducing tissue formation, repairing a tissue defect or regeneration tissue of this invention further comprise the step of administering to the target locus a bone morphogenic protein. In some embodiments, the bone morphogenic protein is administered as a nucleic acid. In some embodiments, the bone morphogenic protein is

administered as a vector comprising a nucleic acid
encoding the bone morphogenic protein operably linked to
an expression control sequence. In some embodiments,
the bone morphogenic protein is administered as a cell

5   comprising a vector comprising a nucleic acid encoding a
bone morphogenic protein operably linked to an
expression control sequence. In some embodiments, the
expression control sequence linked to the BMP nucleic
acid comprises a constitutive promoter. In some

10   embodiments, the expression control sequence linked to
the BMP nucleic acid comprises an inducible promoter.
[0020]   The bone morphogenic protein according to this
invention includes, but is not limited to, OP-1 (BMP-7),
OP-2, OP-3, COP-1, COP-3, COP-4, COP-5, COP-7, COP-16,

15   BMP-2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, BMP-9, BMP-
10, BMP-11, CDMP-3 (BMP-12), CDMP-2 (BMP-13), CDMP-1
(BMP-14), BMP-15, BMP-16, BMP-17, BMP-18, GDF-1, GDF-2,
GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-
11, GDF-12, MP121, dorsalin-1, DPP, Vg-1, Vgr-1, 60A

20   protein, NODAL, UNIVIN, SCREW, ADMP, NEURAL, and
fragments thereof. In some embodiments, one BMP is
administered. In some embodiments, more than one BMP is
administered. In some embodiments, two BMPs are
administered. In some embodiments, the first BMP is OP-

25   1 and the second BMP is CDMP-1 or GDF-5. In a preferred
embodiment, the BMP is OP-1. In another preferred
embodiment, the BMP is CDMP-1 or GDF-5.

Brief Description of the Drawings

[0021]   Figure 1 is a Western blot analysis for Smad5
30   protein in C2C12 cells following treatment with OP-1 and
CDMP-1. Lane 1 is the Smad5 levels in control C2C12
cells. Lane 2 is the Smad5 levels in CDMP-1 treated

(200 ng/ml) C2C12 cells. Lane 3 is the Smad5 levels in
OP-1 treated (100 ng/ml) C2C12 cells. Lane 4 is the
Smad5 levels in cells treated with both OP-1 (100 ng/ml)
and CDMP-1 (200 ng/ml).

5   [0022]   Figure 2 is a plasmid map of pW24 containing
the OP-1 gene.

Detailed Description of the Invention

[0023]   In order that the invention herein described
may be fully understood, the following detailed

10   description is set forth.
[0024]   Unless defined otherwise, all technical and
scientific terms used herein have the same meaning as
those commonly understood by one of ordinary skill in
the art to which this invention belongs. Although

15   methods and materials similar or equivalent to those
described herein can be used in the practice or testing
of the present invention, suitable methods and materials
are described below. The materials, methods and
examples are illustrative only, and are not intended to

20   be limiting. All publications, patents and other
documents mentioned herein are incorporated by reference
in their entirety.
[0025]   Throughout this specification, the word
"comprise" or variations such as "comprises" or

25   "comprising" will be understood to imply the inclusion
of a stated integer or groups of integers but not the
exclusion of any other integer or group of integers.
[0026]   In order to further define the invention, the
following terms and definitions are provided herein.

30   [0027]   The term "defect" or "defect site," refers to
a disruption of the specified tissue. A defect can
assume the configuration of a "void", which is

understood to mean a three-dimensional defect such as,
for example, a gap, cavity, hole or other substantial
disruption in the structural integrity of the tissue
(e.g., bone, chondral, osteochondral, neural, ligament,
tendon). Moreover, a defect can also be a detachment of
the tendon or ligament from its point of attachment to
bone, cartilage or muscle. In certain embodiments, the
defect is such that it is incapable of endogenous or
spontaneous repair. A defect can be the result of
accident, disease, and/or surgical manipulation.

[0028]   The term "target locus" refers to the site
(e.g., a defect) in any tissue that is in need of repair
or regeneration. The target locus need not be a defect
sit. It may be any site where bone, cartilage, tendon,
ligament or neural tissue regeneration is desired.

[0029]   The term "repair" refers to new tissue
formation which is sufficient to at least partially fill
the void or structural discontinuity at the defect site.
Repair does not, however, mean, or otherwise
necessitate, a process of complete healing or a
treatment, which is 100% effective at restoring a defect
to its pre-defect physiological/structural/
mechanical state.

[0030]   The term "therapeutically effective amount"
refers to an amount effective to repair, regenerate,
promote, accelerate, prevent degradation, or form
tissue.

[0031]   The term "patient" refers to an animal,
including a mammal (e.g., a human).

[0032]   The term "bone morphogenic protein (BMP)"
refers to a protein belonging to the BMP family of the
TGF-β superfamily of proteins (BMP family) based on DNA
and amino acid sequence homology. A protein belongs to

the BMP family according to this invention when it has
at least 50% amino acid sequence identity with at least
one known BMP family member within the conserved C-
terminal cysteine-rich domain, which characterizes the
5   BMP protein family. Preferably, the protein has at
least 70% amino acid sequence identity with at least one
known BMP family member within the conserved C-terminal
cysteine rich domain. Members of the BMP family may
have less than 50% DNA or amino acid sequence identity
10 overall. Bone morphogenic proteins may be monomeric,
homo- or hetero-dimeric. Bone morphogenic proteins
include osteogenic proteins.

[0033]   Bone morphogenic proteins are capable of
inducing progenitor cells to proliferate and/or to
15 initiate differentiation pathways that lead to
cartilage, bone, tendon, ligament or other types of
tissue formation depending on local environmental cues,
and thus bone morphogenic proteins may behave
differently in different surroundings. For example, a
20 bone morphogenic protein may induce bone tissue at one
treatment site and cartilage tissue at a different
treatment site. Bone morphogenic proteins include full
length proteins as well as fragments thereof.

[0034]   The term "osteogenic protein (OP)" refers to a
25 bone morphogenic protein that is capable of inducing a
progenitor cell to form cartilage and/or bone. The bone
may be intramembranous bone or endochondral bone. Most
osteogenic proteins are members of the BMP protein
family and are thus also BMPs. As described elsewhere
30 herein, the class of proteins is typified by human
osteogenic protein (hOP-1). Other osteogenic proteins
useful in the practice of the invention include but are
not limited to, osteogenically active forms of OP-1, OP-

2, OP-3, COP-1, COP-3, COP-4, COP-5, COP-7, COP-16, BMP-
2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, BMP-9, BMP-10,
BMP-11, CDMP-3 (BMP-12), CDMP-2 (BMP-13), CDMP-1 (BMP-
14), BMP-15, BMP-16, BMP-17, BMP-18, GDF-1, GDF-2, GDF-

5   3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11,
GDF-12, MP121, dorsalin-1, DPP, Vg-1, Vgr-1, 60A
protein, NODAL, UNIVIN, SCREW, ADMP, NEURAL,
conservative amino acid sequence variants thereof having
osteogenic activity and fragments thereof. In one

10 currently preferred embodiment, osteogenic protein
includes any one of: OP-1, CDMP-1, CDMP-2, CDMP-3, GDF-
5, GDF-6, GDF-7, amino acid sequence variants and
homologs thereof, including species homologs thereof and
fragments thereof. Particularly preferred osteogenic

15 proteins are those comprising an amino acid sequence
having at least 70% homology with the C-terminal 102-106
amino acids, defining the conserved seven cysteine
domain, of, e.g., human OP-1. Certain preferred
embodiments of the instant invention comprise the

20 osteogenic protein, OP-1. As further described
elsewhere herein, the osteogenic proteins suitable for
use with this invention can be identified by means of
routine experimentation using the art-recognized
bioassay described by Reddi and Sampath (Sampath *et al.*,

25 *Proc. Natl. Acad. Sci.*, 84, pp. 7109-13, incorporated
herein by reference).

[0035]   Proteins useful in this invention include
eukaryotic proteins identified as osteogenic proteins
(see U.S. Patent 5,011,691, incorporated herein by

30 reference), such as the OP-1, OP-2, OP-3 and CBMP-2
proteins, as well as amino acid sequence-related
proteins, such as DPP (from Drosophila), Vg1 (from
Xenopus), Vgr-1 (from mouse), GDF-1 (from humans, see

Lee, *PNAS*, 88, pp. 4250-4254 (1991)), 60A (from

Drosophila, see Wharton *et al.*, *PNAS*, 88, pp. 9214-9218

(1991)), dorsalin-1 (from chick, see Basler *et al.*,

Cell, 73, pp. 687-702 (1993) and GenBank accession

5   number L12032) and GDF-5 (from mouse, see Storm *et al.*,

Nature, 368, pp. 639-643 (1994)). The teaching of the

above references are incorporated herein by reference.

BMP-3 is also preferred. Additional useful proteins

include biosynthetic morphogenic constructs disclosed in

10   U.S. Pat. No. 5,011,691, incorporated herein by

reference, e.g., COP-1, COP-3, COP-4, COP-5, COP-7 and

COP-16, as well as other proteins known in the art.

Still other proteins include osteogenically active forms

of BMP-3b (see Takao, *et al.*, *Biochem. Biophys. Res.*

15   *Comm.*, 219, pp. 656-662 (1996)). BMP-9 (see WO

95/33830), BMP-15 (see WO 96/35710), BMP-12 (see WO

95/16035), CDMP-1 (see WO 94/12814), CDMP-2 (see WO

94/12814), BMP-10 (see WO 94/26893), GDF-1 (see WO

92/00382), GDF-10 (see WO95/10539), GDF-3 (see WO

20   94/15965) and GDF-7 (see WO95/01802). The teachings of

the above references are incorporated herein by

reference. BMPs (identified by sequence homology) must

have demonstrable osteogenic activity in a functional

bioassay to be osteogenic proteins according to this

25   invention.

[0036]   The term "amino acid sequence homology" is

understood to include both amino acid sequence identity

and similarity. Homologous sequences share identical

and/or similar amino acid residues, where similar

30   residues are conservative substitutions for, or "allowed

point mutations" of, corresponding amino acid residues

in an aligned reference sequence. Thus, a candidate

polypeptide sequence that shares 70% amino acid homology

with a reference sequence is one in which any 70% of the
aligned residues are either identical to, or are
conservative substitutions of, the corresponding
residues in a reference sequence. Certain particularly
5   preferred bone morphogenic polypeptides share at least
60%, and preferably 70% amino acid sequence identity
with the C-terminal 102-106 amino acids, defining the
conserved seven-cysteine domain of human OP-1 and
related proteins.

10   [0037]   Amino acid sequence homology can be determined
by methods well known in the art. For instance, to
determine the percent homology of a candidate amino acid
sequence to the sequence of the seven-cysteine domain,
the two sequences are first aligned. The alignment can
15   be made with, *e.g.*, the dynamic programming algorithm
described in Needleman *et al.*, J. Mol. Biol., 48,
pp. 443 (1970), and the Align Program, a commercial
software package produced by DNAstar, Inc. The
teachings by both sources are incorporated by reference
20   herein. An initial alignment can be refined by
comparison to a multi-sequence alignment of a family of
related proteins. Once the alignment is made and
refined, a percent homology score is calculated. The
aligned amino acid residues of the two sequences are
25   compared sequentially for their similarity to each
other. Similarity factors include similar size, shape
and electrical charge. One particularly preferred
method of determining amino acid similarities is the
PAM250 matrix described in Dayhoff *et al.*, Atlas of
30   Protein Sequence and Structure, 5, pp. 345-352 (1978 &
Supp.), which is incorporated herein by reference. A
similarity score is first calculated as the sum of the
aligned pair wise amino acid similarity scores.

Insertions and deletions are ignored for the purposes of
percent homology and identity. Accordingly, gap
penalties are not used in this calculation. The raw
score is then normalized by dividing it by the geometric

5   mean of the scores of the candidate sequence and the
seven-cysteine domain. The geometric mean is the square
root of the product of these scores. The normalized raw
score is the percent homology.

[0038]   The term "conservative substitutions" refers

10   to residues that are physically or functionally similar
to the corresponding reference residues. That is, a
conservative substitution and its reference residue have
similar size, shape, electric charge, chemical
properties including the ability to form covalent or

15   hydrogen bonds, or the like. Preferred conservative
substitutions are those fulfilling the criteria defined
for an accepted point mutation in Dayhoff *et al.*, *supra*.
Examples of conservative substitutions are substitutions
within the following groups: (a) valine, glycine; (b)

20   glycine, alanine; (c) valine, isoleucine, leucine; (d)
aspartic acid, glutamic acid; (e) asparagine, glutamine;
(f) serine, threonine; (g) lysine, arginine, methionine;
and (h) phenylalanine, tyrosine. The term "conservative
variant" or "conservative variation" also includes the

25   use of a substituting amino acid residue in place of an
amino acid residue in a given parent amino acid
sequence, where antibodies specific for the parent
sequence are also specific for, i.e., "cross-react" or
"immuno-react" with, the resulting substituted

30   polypeptide sequence.

[0039]   The term "fragment thereof" or "fragment"
refers to a stretch of at least about 5 amino acid
residues. In some embodiments, this term refers to a

stretch of at least about 10 amino acid residues. In other embodiments, it refers to a stretch of at least about 15 to 20 amino acid residues. The fragments may be naturally derived or synthetically generated. To be active, any fragment must have sufficient length to display biological activity.

Methods Using Smads

[0040]   The present invention provides a method of inducing the expression of a Smad in a cell or tissue comprising the step of contacting the cell or tissue capable of expressing the Smad with a bone morphogenic protein.

[0041]   This invention also provides gene therapy methods for inducing tissue formation at a target locus, repairing a tissue defect or regenerating tissue at a target locus using Smads. In some embodiments, the methods comprise the step of administering to the target locus a nucleic acid encoding a Smad. In some embodiments, the methods comprise the step of administering to the target locus a vector comprising a nucleic acid encoding a Smad operably linked to an expression control sequence. In some embodiments, the methods comprise the step of administering a cell comprising a vector comprising a nucleic acid encoding a Smad operably linked to an expression control sequence. In some embodiments, the expression control sequence operably linked to a Smad nucleic acid comprises an inducible promoter. In some embodiments, the expression control sequence operably linked to a Smad nucleic acid comprises a constitutive promoter.

[0042]   A Smad according to the present invention is a R-Smad. R-Smads includes, but are not limited to,

Smad1, Smad2, Smad3, Smad5, Smad8 or fragments thereof.
In a preferred embodiment, the Smad is Smad5. In
another embodiment the Smad is recombinant.

[0043]   In some embodiments, the gene therapy methods

5   further comprise the step of administering to the target
locus a pharmaceutically effective amount of a BMP. In
some embodiments, the methods further comprise the step
of administering a nucleic acid encoding a BMP. In some
embodiments, the methods further comprise the step of

10   administering a vector comprising a nucleic acid
encoding a BMP operably linked to an expression control
sequence. In some embodiments, the methods further
comprise the step of administering a cell comprising a
vector comprising a nucleic acid encoding a BMP operably

15   linked to an expression control sequence. In some
embodiments, the expression control sequence operably
linked to a BMP nucleic acid comprises an inducible
promoter. In some embodiments, the expression control
sequence operably linked to a BMP nucleic acid comprises

20   a constitutive promoter.

[0044]   The BMPs according to the invention include
but are not limited to, OP-1 (BMP-7), OP-2, OP-3, COP-1,
COP-3, COP-4, COP-5, COP-7, COP-16, BMP-2, BMP-3, BMP-
3b, BMP-4, BMP-5, BMP-6, BMP-9, BMP-10, BMP-11, CDMP-3

25   (BMP-12), CDMP-2 (BMP-13), CDMP-1 (BMP-14), BMP-15, BMP-
16, BMP-17, BMP-18, GDF-1, GDF-2, GDF-3, GDF-5, GDF-6,
GDF-7, GDF-8, GDF-9, GDF-10, GDF-11, GDF-12, MP121,
dorsalin-1, DPP, Vg-1, Vgr-1, 60A protein, NODAL,
UNIVIN, SCREW, ADMP, and NEURAL. (see *infra*, for

30   discussion of BMPs). In a preferred embodiment, the BMP
is OP-1 (BMP-7). In another preferred embodiment, the
BMP is CDMP-1 or GDF-5.

[0045] In some embodiments, more than one BMP is administered. In one preferred embodiment, two BMPs are administered. In yet another preferred embodiment, the first BMP is OP-1 and the second BMP is CDMP-1 or GDF-5. In another embodiment three BMPs are administered. In some embodiments, the BMP is recombinant.

[0046] In some embodiments, the gene therapy methods of this invention further comprise the step of administering a serine/threonine kinase receptor. In some embodiments, the methods of this invention further comprise the step of administering to the target locus a nucleic acid encoding a serine/threonine kinase receptor. In some embodiments, the methods of this invention further comprise the step of administering to the target locus a vector comprising a nucleic acid encoding a serine/threonine kinase receptor operably linked to an expression control sequence. In some embodiments, the methods of this invention further comprise the step of administering to the target locus a cell comprising a vector comprising a nucleic acid encoding a serine/threonine kinase receptor operably linked to an expression control sequence. In some embodiments, the serine/threonine kinase receptor is selected from the group consisting of type I and type II receptors. In some embodiments, only a type I receptor is used. In some embodiments, only a type II receptors is used. In some embodiments both type I and type II receptors are used. Preferably the type I and type II receptors are recombinant. In some embodiments, the expression control sequence operably linked to a serine/threonine kinase receptor nucleic acid comprises an inducible promoter. In some embodiments, the expression control sequence operably linked to a

serine/threonine kinase receptor nucleic acid comprises
a constitutive promoter.

[0047]   In some embodiments, the type I receptor is an
activin receptor-like kinase (ALK). The ALKs according
to this invention include, but are not limited to ALK-1,
ALK-2, ALK-3, ALK-4, ALK-5, ALK-6, ALK-7, and fragments
thereof. Preferred ALKs are ALK-2, ALK-3 and ALK-6.

Bone Morphogenic Protein (BMP) Family

[0048]   The BMP family, named for its representative
bone morphogenic/osteogenic protein family members,
belongs to the TGF-β protein superfamily. Of the
reported "BMPs" (BMP-1 to BMP-18), isolated primarily
based on sequence homology, all but BMP-1 remain
classified as members of the BMP family of morphogenic
proteins (Ozkaynak *et al.*, *EMBO J.*, 9, pp. 2085-93
(1990)).

[0049]   The BMP family includes other structurally-
related members which are bone morphogenic proteins,
including the *drosophila* decapentaplegic gene complex
(DPP) products, the Vg1 product of *Xenopus laevis* and
its murine homolog, Vgr-1 (see, *e.g.*, Massagué, *Annu.*
Rev. Cell Biol., 6, pp. 597-641 (1990), incorporated
herein by reference).

[0050]   The *Drosophila* DPP and *Xenopus* Vg-1 gene
products are 50% identical to each other (and 35-40%
identical to TGF-ß). Both the Dpp and Vg-1 products are
morphogenic proteins that participate in early
patterning events during embryogenesis of their
respective hosts. These products appear to be most
closely related to mammalian bone morphogenetic proteins
BMP-2 and BMP-4, whose C-terminal domains are 75%
identical with that of Dpp.

[0051]   The C-terminal domains of BMP-3, BMP-5, BMP-6, and OP-1 (BMP-7) are about 60% identical to that of BMP-2, and the C-terminal domains of BMP-6 and OP-1 are 87% identical. BMP-6 is likely the human homolog of the murine Vgr-1 (Lyons *et al., Proc. Natl. Acad. Sci. U.S.A.*, 86, pp. 4554-59 (1989)); the two proteins are 92% identical overall at the amino acid sequence level (U.S. Patent No. 5,459,047, incorporated herein by reference). BMP-6 is 58% identical to the *Xenopus* Vg-1 product.

[0052]   The naturally occurring bone morphogenic proteins share substantial amino acid sequence homology in their C-terminal regions (domains). Typically, the above-mentioned naturally occurring osteogenic proteins are translated as a precursor, having an N-terminal signal peptide sequence typically less than about 30 residues, followed by a "pro" domain that is cleaved to yield the mature C-terminal domain of approximately 100-140 amino acids. The signal peptide is cleaved rapidly upon translation, at a cleavage site that can be predicted in a given sequence using the method of Von Heijne, *Nucleic Acids Research*, 14, pp. 4683-4691 (1986). The pro domain typically is about three times larger than the fully processed mature C-terminal domain.

[0053]   Another characteristic of the BMP protein family members is their ability to dimerize. Several bone-derived osteogenic proteins (OPs) and BMPs are found as homo- and heterodimers in their active forms. The ability of OPs and BMPs to form heterodimers may confer additional or altered morphogenic inductive capabilities on bone morphogenic proteins. Heterodimers may exhibit qualitatively or quantitatively different

binding affinities than homodimers for OP and BMP
receptor molecules. Altered binding affinities may in
turn lead to differential activation of receptors that
mediate different signaling pathways, which may

5   ultimately lead to different biological activities or
outcomes. Altered binding affinities could also be
manifested in a tissue or cell type-specific manner,
thereby inducing only particular progenitor cell types
to undergo proliferation and/or differentiation.

10   [0054]   In one preferred embodiment of this invention,
the BMPs independently comprise a pair of subunits
disulfide bonded to produce a dimeric species, wherein
at least one of the subunits comprises a recombinant
peptide belonging to the BMP protein family. In another

15   preferred embodiment of this invention, the BMPs
independently comprise a pair of subunits that produce a
dimeric species formed through non-covalent
interactions, wherein at least one of the subunits
comprises a recombinant peptide belonging to the BMP

20   protein family. Non-covalent interactions include Van
der Waals, hydrogen bond, hydrophobic and electrostatic
interactions. The dimeric species may be a homodimer or
heterodimer and is capable of inducing cell
proliferation and/or tissue formation. In some

25   embodiments, the BMPs are each independently monomers.
[0055]   In preferred embodiments, the pair of
morphogenic polypeptides have amino acid sequences each
comprising a sequence that shares a defined relationship
with an amino acid sequence of a reference morphogen.

30   Herein, preferred osteogenic polypeptides share a
defined relationship with a sequence present in
osteogenically active human OP-1, SEQ ID NO: 1.
However, any one or more of the naturally occurring or

biosynthetic sequences disclosed herein similarly could
be used as a reference sequence. Preferred osteogenic
polypeptides share a defined relationship with at least
the C-terminal six cysteine domain of human OP-1,

5   residues 335-431 of SEQ ID NO: 1. Preferably,
osteogenic polypeptides share a defined relationship
with at least the C-terminal seven cysteine domain of
human OP-1, residues 330-431 of SEQ ID NO: 1. That is,
preferred polypeptides in a dimeric protein with bone

10   morphogenic activity each comprise a sequence that
corresponds to a reference sequence or is functionally
equivalent thereto.

       [0056]   Functionally equivalent sequences include
functionally equivalent arrangements of cysteine

15   residues disposed within the reference sequence,
including amino acid insertions or deletions which alter
the linear arrangement of these cysteines, but do not
materially impair their relationship in the folded
structure of the dimeric morphogen protein, including

20   their ability to form such intra- or inter-chain
disulfide bonds as may be necessary for morphogenic
activity. Functionally equivalent sequences further
include those wherein one or more amino acid residues
differs from the corresponding residue of a reference

25   sequence, e.g., the C-terminal seven cysteine domain
(also referred to herein as the conserved seven cysteine
skeleton) of human OP-1, provided that this difference
does not destroy bone morphogenic activity.
Accordingly, conservative substitutions of corresponding

30   amino acids in the reference sequence are preferred.
Particularly preferred conservative substitutions are
those fulfilling the criteria defined for an accepted

point mutation in Dayhoff *et al.*, *supra*, the teachings
of which are incorporated by reference herein.

[0057]   The osteogenic protein OP-1 has been described
(see, *e.g.*, Oppermann *et al.*, U. S. Patent No.
5,354,557, incorporated herein by reference). Natural-
sourced osteogenic protein in its mature, native form is
a glycosylated dimer typically having an apparent
molecular weight of about 30-36 kDa as determined by
SDS-PAGE. When reduced, the 30 kDa protein gives rise
to two glycosylated peptide subunits having apparent
molecular weights of about 16 kDa and 18 kDa. The
unglycosylated protein, which also has osteogenic
activity, has an apparent molecular weight of about 27
kDa. When reduced, the 27 kDa protein gives rise to two
unglycosylated polypeptides, having molecular weights of
about 14 kDa to 16 kDa, capable of inducing endochondral
bone formation in a mammal. Osteogenic proteins may
include forms having varying glycosylation patterns,
varying N-termini, and active truncated or mutated forms
of native protein.

[0058]   As described above, particularly useful
sequences include those comprising the C-terminal 96 or
102 amino acid sequences of DPP (from Drosophila), Vg1
(from Xenopus), Vgr-1 (from mouse), the OP-1 and OP-2
proteins, (see U.S. Pat. No. 5,011,691 and Oppermann *et
al.*, incorporated herein by reference), as well as the
proteins referred to as BMP-2, BMP-3, BMP-4 (see WO
88/00205, U.S. Patent No. 5,013,649 and WO 91/18098,
incorporated herein by reference), BMP-5 and BMP-6 (see
WO 90/11366, PCT/US90/01630, incorporated herein by
reference), BMP-8 and BMP-9.

[0059]   Preferred BMPs of this invention comprise at
least one polypeptide selected from the group consisting

of OP-1 (BMP-7), OP-2, OP-3, COP-1, COP-3, COP-4, COP-5, COP-7, COP-16, BMP-2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, BMP-9, BMP-10, BMP-11, CDMP-3 (BMP-12), CDMP-2 (BMP-13), CDMP-1 (BMP-14), BMP-15, BMP-16, BMP-17, BMP-18, GDF-1, GDF-2, GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11, GDF-12, MP121, dorsalin-1, DPP, Vg-1, Vgr-1, 60A protein, NODAL, UNIVIN, SCREW, ADMP, NEURAL and amino acid sequence variants and homologs thereof, including species homologs thereof and fragments thereof. In some embodiments, one BMP is used. In some embodiments, more than one BMP is used. In some embodiments, two BMPs are used. In some embodiments, three BMPs are used. In some embodiments, the first BMP is OP-1 (BMP-7) or a fragment thereof, and the second BMP is selected from the group consisting of CDMP-1, CDMP-2, CDMP3, GDF-5, GDF-6, GDF-7 and fragments thereof. In some embodiments, the second BMP is CDMP-1, GDF-5 or a fragment thereof. In some embodiments, the first BMP is OP-1 and the second BMP is CDMP-2 or GDF-5.

[0060]   Publications disclosing these sequences, as well as their chemical and physical properties, include: OP-1 and OP-2 (U.S. Patent No. 5,011,691; U.S. Patent No. 5,266,683; Ozkaynak et al., EMBO J., 9, pp. 2085-2093 (1990); OP-3 (WO 94/10203 (PCT US93/10520)), BMP-2, BMP-3, BMP-4, (WO 88/00205; Wozney et al. Science, 242, pp. 1528-1534 (1988)), BMP-5 and BMP-6, (Celeste et al., PNAS, 87, 9843-9847 (1991)), Vgr-1 (Lyons et al., PNAS, 86, pp. 4554-4558 (1989)); DPP (Padgett et al. Nature, 325, pp. 81-84 (1987)); Vg-1 (Weeks, Cell, 51, pp. 861-867 (1987)); BMP-9 (WO95/33830 (PCT/US95/07084); BMP-10 (WO 94/26893 (PCT/US94/05290); BMP-11 (WO 94/26892 (PCT/US94/05288); BMP-12 (WO95/16035 (PCT/US94/14030); BMP-13 (WO95/16035 (PCT/US94/14030);

GDF-1 (WO 92/00382 (PCT/US91/04096) and Lee *et al.* *PNAS*,
88, pp. 4250-4254 (1991); GDF-8 (WO 94/21681
(PCT/US94/03019); GDF-9 (WO 94/15966 (PCT/US94/00685);
GDF-10 (WO 95/10539 (PCT/US94/11440); GDF-11 (WO
5   96/01845 (PCT/US95/08543); BMP-15 (WO 96/36710
(PCT/US96/06540); MP-121 (WO 96/01316 (PCT/EP95/02552);
GDF-5 (CDMP-1, MP52) (WO 94/15949 (PCT/US94/00657) and
WO 96/14335 (PCT/US94/12814) and WO 93/16099
(PCT/EP93/00350)); GDF-6 (CDMP-2, BMP13) (WO 95/01801
10 (PCT/US94/07762) and WO 96/14335 and WO 95/10635
(PCT/US94/14030)); GDF-7 (CDMP-3, BMP12) (WO 95/10802
(PCT/US94/07799) and WO 95/10635 (PCT/US94/14030)). The
above publications are incorporated herein by reference.

[0061]   In another embodiment of this invention, the
15 BMPs may be prepared synthetically. BMPs prepared
synthetically may be native, or may be non-native
proteins, i.e., those not otherwise found in nature.
Non-native osteogenic proteins have been synthesized
using a series of consensus DNA sequences (U.S. Patent
20 No. 5,324,819, incorporated herein by reference). These
consensus sequences were designed based on partial amino
acid sequence data obtained from natural osteogenic
products and on their observed homologies with other
genes reported in the literature having a presumed or
25 demonstrated developmental function.

[0062]   Several of the biosynthetic consensus
sequences (called consensus osteogenic proteins or
"COPs") have been expressed as fusion proteins in
prokaryotes. Purified fusion proteins may be cleaved,
30 refolded, implanted in an established animal model and
shown to have bone- and/or cartilage-inducing activity.
The currently preferred synthetic osteogenic proteins
comprise two synthetic amino acid sequences designated

COP-5 (SEQ. ID NO: 2) and COP-7 (SEQ. ID NO: 3).
Oppermann *et al.*, U. S. Patent Nos. 5,011,691 and
5,324,819, which are incorporated herein by reference,
describe the amino acid sequences of COP-5 and COP-7 as
shown below:

```
COP5      LYVDFS-DVGWDDWIVAPPGYQAFYCHGECPFPLAD
COP7      LYVDFS-DVGWNDWIVAPPGYHAFYCHGECPFPLAD


COP5      HFNSTN--H-AVVQTLVNSVNSKI--PKACCVPTELSA
COP7      HLNSTN--H-AVVQTLVNSVNSKI--PKACCVPTELSA


COP5      ISMLYLDENEKVVLKYNQEMVVEGCGCR
COP7      ISMLYLDENEKVVLKYNQEMVVEGCGCR
```

[0063]   In these amino acid sequences, the dashes (-)
are used as fillers only to line up comparable sequences
in related proteins. Differences between the aligned
amino acid sequences are highlighted.

[0064]   The DNA and amino acid sequences of these and
other BMP family members are published and may be used
by those of skill in the art to determine whether a
newly identified protein belongs to the BMP family.

[0065]   In certain preferred embodiments, the BMPs
useful herein independently include those in which the
amino acid sequences comprise a sequence sharing at
least 70% amino acid sequence homology or "similarity",
preferably 80%, more preferably 90%, even more
preferably 95%, even more preferably 98% homology or
similarity, with a reference bone morphogenic protein
selected from the foregoing naturally occurring
proteins. Preferably, the reference protein is human
OP-1, and the reference sequence thereof is the C-
terminal seven cysteine domain present in osteogenically

active forms of human OP-1, residues 330-431 of SEQ ID
NO: 1. In some embodiments, the BMP comprises a dimeric
protein having an amino acid sequence having at least
70% homology within the C-terminal 102-106 amino acids
5   of human OP-1. In certain embodiments, a polypeptide
suspected of being functionally equivalent to a
reference BMP polypeptide is aligned therewith using the
method of Needleman, *et al.*, *supra*, implemented
conveniently by computer programs such as the Align
10 program (DNAstar, Inc.). As noted above, internal gaps
and amino acid insertions in the candidate sequence are
ignored for purposes of calculating the defined
relationship, conventionally expressed as a level of
amino acid sequence homology or identity, between the
15 candidate and reference sequences. In one preferred
embodiment, the reference sequence is OP-1. In another
preferred embodiment, the reference sequence is selected
from CDMP-1, CDMP-2 or CDMP-3. Bone morphogenic
proteins useful herein accordingly include allelic,
20 phylogenetic counterpart and other variants of the
preferred reference sequence, whether naturally-
occurring or biosynthetically produced (*e.g.*, including
"muteins" or "mutant proteins"), as well as novel
members of the general morphogenic family of proteins,
25 including those set forth and identified above. Certain
particularly preferred bone morphogenic polypeptides
share at least 60% amino acid identity with the
preferred reference sequence of human OP-1, still more
preferably at least 65% amino acid identity therewith.
30 [0066]   In another embodiment, useful BMPs include
those sharing the conserved seven cysteine domain and
sharing at least 70% amino acid sequence homology
(similarity) within the C-terminal active domain, as

defined herein. In still another embodiment, the BMPs
of the invention can be defined as osteogenically active
proteins having any one of the generic sequences defined
herein, including OPX (SEQ ID NO: 4) and Generic

5   Sequences 7 (SEQ ID NO: 5) and 8 (SEQ ID NO: 6), or
Generic Sequences 9 (SEQ ID NO: 7) and 10 (SEQ ID NO:
8).

[0067]   The family of bone morphogenic polypeptides
useful in the present invention, and members thereof,

10   can be defined by a generic amino acid sequence. For
example, Generic Sequence 7 (SEQ ID NO: 5) and Generic
Sequence 8 (SEQ ID NO: 6) are 97 and 102 amino acid
sequences, respectively, and accommodate the homologies
shared among preferred protein family members identified

15   to date, including at least OP-1, OP-2, OP-3, CBMP-2A,
CBMP-2B, BMP-3, 60A, DPP, Vg1, BMP-5, BMP-6, Vgr-1, and
GDF-1. The amino acid sequences for these proteins are
described herein and/or in the art, as summarized above.
The generic sequences include both the amino acid

20   identity shared by these sequences in the C-terminal
domain, defined by the six and seven cysteine skeletons
(Generic Sequences 7 and 8, respectively), as well as
alternative residues for the variable positions within
the sequence. The generic sequences provide an

25   appropriate cysteine skeleton where inter- or
intramolecular disulfide bonds can form, and contain
certain critical amino acids likely to influence the
tertiary structure of the folded proteins. In addition,
the generic sequences allow for an additional cysteine

30   at position 36 (Generic Sequence 7) or position 41
(Generic Sequence 8), thereby encompassing the
morphogenically active sequences of OP-2 and OP-3.

Generic Sequence 7

```
                      Leu  Xaa  Xaa  Xaa  Phe  Xaa  Xaa
                      1                   5
     Xaa  Gly  Trp  Xaa  Xaa  Xaa  Xaa  Xaa  Xaa  Pro
               10                       15
     Xaa  Xaa  Xaa  Xaa  Ala  Xaa  Tyr  Cys  Xaa  Gly
               20                       25
     Xaa  Cys  Xaa  Xaa  Pro  Xaa  Xaa  Xaa  Xaa  Xaa
               30                       35
     Xaa  Xaa  Xaa  Asn  His  Ala  Xaa  Xaa  Xaa  Xaa
               40                       45
     Xaa  Xaa  Xaa  Xaa  Xaa  Xaa  Xaa  Xaa  Xaa  Xaa
               50                       55
     Xaa  Xaa  Xaa  Cys  Cys  Xaa  Pro  Xaa  Xaa  Xaa
               60                       65
     Xaa  Xaa  Xaa  Xaa  Xaa  Leu  Xaa  Xaa  Xaa  Xaa
               70                       75
     Xaa  Xaa  Xaa  Val  Xaa  Leu  Xaa  Xaa  Xaa  Xaa
               80                       85
        Xaa  Met  Xaa  Val  Xaa  Xaa  Cys  Xaa  Cys  Xaa
                  90                       95
```

wherein each Xaa independently is selected from a group

5   of one or more specified amino acids defined as follows:
"res." means "residue" and Xaa at res.2 = (Tyr or Lys);
Xaa at res.3 = Val or Ile); Xaa at res.4 = (Ser, Asp or
Glu); Xaa at res.6 = (Arg, Gln, Ser, Lys or Ala); Xaa at
res.7 = (Asp or Glu); Xaa at res.8 = (Leu, Val or Ile);

10   Xaa at res. 11 = (Gln, Leu, Asp, His, Asn or Ser); Xaa
at res.12 = (Asp, Arg, Asn or Glu); Xaa at res.13 = (Trp
or Ser); Xaa at res.14 = (Ile or Val); Xaa at res.15 =
(Ile or Val); Xaa at res.16 (Ala or Ser); Xaa at res.18
= (Glu, Gln, Leu, Lys, Pro or Arg); Xaa at res.19 = (Gly

15   or Ser); Xaa at res.20 = (Tyr or Phe); Xaa at res.21 =
(Ala, Ser, Asp, Met, His, Gln, Leu or Gly); Xaa at
res.23 = (Tyr, Asn or Phe); Xaa at res.26 = (Glu, His,
Tyr, Asp, Gln, Ala or Ser); Xaa at res.28 = (Glu, Lys,
Asp, Gln or Ala); Xaa at res.30 = (Ala, Ser, Pro, Gln,

Ile or Asn); Xaa at res.31 = (Phe, Leu or Tyr); Xaa at res.33 = (Leu, Val or Met); Xaa at res.34 = (Asn, Asp, Ala, Thr or Pro); Xaa at res.35 = (Ser, Asp, Glu, Leu, Ala or Lys); Xaa at res.36 = (Tyr, Cys, His, Ser or

5 Ile); Xaa at res.37 = (Met, Phe, Gly or Leu); Xaa at res.38 = (Asn, Ser or Lys); Xaa at res.39 = (Ala, Ser, Gly or Pro); Xaa at res.40 = (Thr, Leu or Ser); Xaa at res.44 = (Ile, Val or Thr); Xaa at res.45 = (Val, Leu, Met or Ile); Xaa at res.46 = (Gln or Arg); Xaa at res.47

10 = (Thr, Ala or Ser); Xaa at res.48 = (Leu or Ile); Xaa at res.49 = (Val or Met); Xaa at res.50 = (His, Asn or Arg); Xaa at res.51 = (Phe, Leu, Asn, Ser, Ala or Val); Xaa at res.52 = (Ile, Met, Asn, Ala, Val, Gly or Leu); Xaa at res.53 = (Asn, Lys, Ala, Glu, Gly or Phe); Xaa at

15 res.54 = (Pro, Ser or Val); Xaa at res.55 = (Glu, Asp, Asn, Gly, Val, Pro or Lys); Xaa at res.56 = (Thr, Ala, Val, Lys, Asp, Tyr, Ser, Gly, Ile or His); Xaa at res.57 = (Val, Ala or Ile); Xaa at res.58 = (Pro or Asp); Xaa at res.59 = (Lys, Leu or Glu); Xaa at res.60 = (Pro, Val

20 or Ala); Xaa at res.63 = (Ala or Val); Xaa at res.65 = (Thr, Ala or Glu); Xaa at res.66 = (Gln, Lys, Arg or Glu); Xaa at res.67 = (Leu, Met or Val); Xaa at res.68 = (Asn, Ser, Asp or Gly); Xaa at res.69 =(Ala, Pro or Ser); Xaa at res.70 = (Ile, Thr, Val or Leu); Xaa at

25 res.71 = (Ser, Ala or Pro); Xaa at res.72 = (Val, Leu, Met or Ile); Xaa at res.74 = (Tyr or Phe); Xaa at res.75 = (Phe, Tyr, Leu or His); Xaa at res.76 = (Asp, Asn or Leu); Xaa at res.77 = (Asp, Glu, Asn, Arg or Ser); Xaa at res.78 = (Ser, Gln, Asn, Tyr or Asp); Xaa at res.79 =

30 (Ser, Asn, Asp, Glu or Lys); Xaa at res.80 = (Asn, Thr or Lys); Xaa at res.82 = (Ile, Val or Asn); Xaa at res.84 = (Lys or Arg); Xaa at res.85 = (Lys, Asn, Gln, His, Arg or Val); Xaa at res.86 = (Tyr, Glu or His); Xaa

at res.87 = (Arg, Gln, Glu or Pro); Xaa at res.88 =
(Asn, Glu, Trp or Asp); Xaa at res.90 = (Val, Thr, Ala
or Ile); Xaa at res.92 = (Arg, Lys, Val, Asp, Gln or
Glu); Xaa at res.93 = (Ala, Gly, Glu or Ser); Xaa at

5   res.95 = (Gly or Ala) and Xaa at res.97 = (His or Arg).

[0068]   Generic Sequence 8 (SEQ ID NO: 6) includes all
of Generic Sequence 7 and in addition includes the
following sequence (SEQ ID NO: 9) at its N-terminus:

SEQ ID NO: 9

Cys   Xaa   Xaa   Xaa   Xaa

1   5

10   Accordingly, beginning with residue 7, each "Xaa" in
Generic Sequence 8 is a specified amino acid defined as
for Generic Sequence 7, with the distinction that each
residue number described for Generic Sequence 7 is
shifted by five in Generic Sequence 8. Thus, "Xaa at

15   res.2 =(Tyr or Lys)" in Generic Sequence 7 refers to Xaa
at res.7 in Generic Sequence 8.   In Generic Sequence 8,
Xaa at res.2 = (Lys, Arg, Ala or Gln); Xaa at res.3 =
(Lys, Arg or Met); Xaa at res.4 = (His, Arg or Gln); and
Xaa at res.5 = (Glu, Ser, His, Gly, Arg, Pro, Thr, or

20   Tyr).

[0069]   In another embodiment, useful osteogenic
proteins include those defined by Generic Sequences 9
and 10, defined as follows.

[0070]   Specifically, Generic Sequences 9 and 10 are

25   composite amino acid sequences of the following
proteins: human OP-1, human OP-2, human OP-3, human BMP-
2, human BMP-3, human BMP-4, human BMP-5, human BMP-6,
human BMP-8, human BMP-9, human BMP-10, human BMP-11,
Drosophila 60A, Xenopus Vg-1, sea urchin UNIVIN, human

30   CDMP-1 (mouse GDF-5), human CDMP-2 (mouse GDF-6, human

BMP-13), human CDMP-3 (mouse GDF-7, human BMP-12), mouse
GDF-3, human GDF-1, mouse GDF-1, chicken DORSALIN, dpp,
Drosophila SCREW, mouse NODAL, mouse GDF-8, human GDF-8,
mouse GDF-9, mouse GDF-10, human GDF-11, mouse GDF-11,
human BMP-15, and rat BMP3b. Like Generic Sequence 7,
Generic Sequence 9 is a 97 amino acid sequence that
accommodates the C-terminal six cysteine skeleton and,
like Generic Sequence 8, Generic Sequence 10 is a 102
amino acid sequence which accommodates the seven
cysteine skeleton.

Generic Sequence 9

Xaa 1	Xaa	Xaa	Xaa	Xaa 5	Xaa	Xaa	Xaa	Xaa	Xaa 10
Xaa	Xaa	Xaa	Xaa	Xaa 15	Xaa	Pro	Xaa	Xaa	Xaa 20
Xaa	Xaa	Xaa	Xaa	Cys 25	Xaa	Gly	Xaa	Cys	Xaa 30
Xaa	Xaa	Xaa	Xaa	Xaa 35	Xaa	Xaa	Xaa	Xaa	Xaa 40
Xaa	Xaa	Xaa	Xaa	Xaa 45	Xaa	Xaa	Xaa	Xaa	Xaa 50
Xaa	Xaa	Xaa	Xaa	Xaa 55	Xaa	Xaa	Xaa	Xaa	Xaa 60
Xaa	Cys	Xaa	Pro	Xaa 65	Xaa	Xaa	Xaa	Xaa	Xaa 70
Xaa	Xaa	Leu	Xaa	Xaa 75	Xaa	Xaa	Xaa	Xaa	Xaa 80
Xaa	Xaa	Xaa	Xaa	Xaa 85	Xaa	Xaa	Xaa	Xaa	Xaa 90
Xaa	Xaa	Xaa	Cys	Xaa 95	Cys	Xaa			

wherein each Xaa is independently selected from a group
of one or more specified amino acids defined as follows:
"res." means "residue" and Xaa at res.1 = (Phe, Leu or
Glu); Xaa at res.2 = (Tyr, Phe, His, Arg, Thr, Lys, Gln,
Val or Glu); Xaa at res.3 = (Val, Ile, Leu or Asp); Xaa
at res.4 = (Ser, Asp, Glu, Asn or Phe); Xaa at res.5 =
(Phe or Glu); Xaa at res.6 = (Arg, Gln, Lys, Ser, Glu,

Ala or Asn); Xaa at res.7 = (Asp, Glu, Leu, Ala or Gln);
Xaa at res.8 = (Leu, Val, Met, Ile or Phe); Xaa at res.9
= (Gly, His or Lys); Xaa at res.10 = (Trp or Met); Xaa
at res.11 = (Gln, Leu, His, Glu, Asn, Asp, Ser or Gly);

5   Xaa at res.12 = (Asp, Asn, Ser, Lys, Arg, Glu or His);
Xaa at res.13 = (Trp or Ser); Xaa at res.14 = (Ile or
Val); Xaa at res.15 = (Ile or Val); Xaa at res.16 =
(Ala, Ser, Tyr or Trp); Xaa at res. 18 = (Glu, Lys, Gln,
Met, Pro, Leu, Arg, His or Lys); Xaa at res.19 = (Gly,

10 Glu, Asp, Lys, Ser, Gln, Arg or Phe); Xaa at res.20 =
(Tyr or Phe); Xaa at res.21 = (Ala, Ser, Gly, Met, Gln,
His, Glu, Asp, Leu, Asn, Lys or Thr); Xaa at res.22 =
(Ala or Pro); Xaa at res.23 = (Tyr, Phe, Asn, Ala or
Arg); Xaa at res.24 = (Tyr, His, Glu, Phe or Arg); Xaa

15 at res.26 = (Glu, Asp, Ala, Ser, Tyr, His, Lys, Arg, Gln
or Gly); Xaa at res.28 = (Glu, Asp, Leu, Val, Lys, Gly,
Thr, Ala or Gln); Xaa at res.30 = (Ala, Ser, Ile, Asn,
Pro, Glu, Asp, Phe, Gln or Leu); Xaa at res.31= (Phe,
Tyr, Leu, Asn, Gly or Arg); Xaa at res.32 = (Pro, Ser,

20 Ala or Val); Xaa at res.33 = (Leu, Met, Glu, Phe or
Val); Xaa at res.34 = (Asn, Asp, Thr, Gly, Ala, Arg, Leu
or Pro); Xaa at res.35 = (Ser, Ala, Glu, Asp, Thr, Leu,
Lys, Gln or His); Xaa at res.36 = (Tyr, His, Cys, Ile,
Arg, Asp, Asn, Lys, Ser, Glu or Gly); Xaa at res.37 =

25 (Met, Leu, Phe, Val, Gly or Tyr); Xaa at res.38 = (Asn,
Glu, Thr, Pro, Lys, His, Gly, Met, Val or Arg); Xaa at
res.39 = (Ala, Ser, Gly, Pro or Phe); Xaa at res.40 =
(Thr, Ser, Leu, Pro, His or Met); Xaa at res.41 = (Asn,
Lys, Val, Thr or Gln); Xaa at res.42 = (His, Tyr or

30 Lys); Xaa at res.43 = (Ala, Thr, Leu or Tyr); Xaa at
res.44 = (Ile, Thr, Val, Phe, Tyr, Met or Pro); Xaa at
res.45 = (Val, Leu, Met, Ile or His); Xaa at res.46 =
(Gln, Arg or Thr); Xaa at res.47 = (Thr, Ser, Ala, Asn

or His); Xaa at res.48 = (Leu, Asn or Ile); Xaa at

res.49 = (Val, Met, Leu, Pro or Ile); Xaa at res.50 =

(His, Asn, Arg, Lys, Tyr or Gln); Xaa at res.51 = (Phe,

Leu, Ser, Asn, Met, Ala, Arg, Glu, Gly or Gln); Xaa at

5   res.52 = (Ile, Met, Leu, Val, Lys, Gln, Ala or Tyr); Xaa

at res.53 = (Asn, Phe, Lys, Glu, Asp, Ala, Gln, Gly, Leu

or Val); Xaa at res.54 = (Pro, Asn, Ser, Val or Asp);

Xaa at res.55 = (Glu, Asp, Asn, Lys, Arg, Ser, Gly, Thr,

Gln, Pro or His); Xaa at res.56 = (Thr, His, Tyr, Ala,

10   Ile, Lys, Asp, Ser, Gly or Arg); Xaa at res.57 = (Val,

Ile, Thr, Ala, Leu or Ser); Xaa at res.58 = (Pro, Gly,

Ser, Asp or Ala); Xaa at res.59 = (Lys, Leu, Pro, Ala,

Ser, Glu, Arg or Gly); Xaa at res.60 = (Pro, Ala, Val,

Thr or Ser); Xaa at res.61 = (Cys, Val or Ser); Xaa at

15   res.63 = (Ala, Val or Thr); Xaa at res.65 = (Thr, Ala,

Glu, Val, Gly, Asp or Tyr); Xaa at res.66 = (Gln, Lys,

Glu, Arg or Val); Xaa at res.67 = (Leu, Met, Thr or

Tyr); Xaa at res.68 = (Asn, Ser, Gly, Thr, Asp, Glu, Lys

or Val); Xaa at res.69 = (Ala, Pro, Gly or Ser); Xaa at

20   res.70 = (Ile, Thr, Leu or Val); Xaa at res.71 = (Ser,

Pro, Ala, Thr, Asn or Gly); Xaa at res.72 = (Val, Ile,

Leu or Met); Xaa at res.74 = (Tyr, Phe, Arg, Thr, Tyr or

Met); Xaa at res.75 = (Phe, Tyr, His, Leu, Ile, Lys, Gln

or Val); Xaa at res.76 = (Asp, Leu, Asn or Glu); Xaa at

25   res.77 = (Asp, Ser, Arg, Asn, Glu, Ala, Lys, Gly or

Pro); Xaa at res.78 = (Ser, Asn, Asp, Tyr, Ala, Gly,

Gln, Met, Glu, Asn or Lys); Xaa at res.79 = (Ser, Asn,

Glu, Asp, Val, Lys, Gly, Gln or Arg); Xaa at res.80 =

(Asn, Lys, Thr, Pro, Val, Ile, Arg, Ser or Gln); Xaa at

30   res.81 = (Val, Ile, Thr or Ala); Xaa at res.82 = (Ile,

Asn, Val, Leu, Tyr, Asp or Ala); Xaa at res.83 = (Leu,

Tyr, Lys or Ile); Xaa at res.84 = (Lys, Arg, Asn, Tyr,

Phe, Thr, Glu or Gly); Xaa at res.85 = (Lys, Arg, His,

Gln, Asn, Glu or Val); Xaa at res.86 = (Tyr, His, Glu or
Ile); Xaa at res.87 = (Arg, Glu, Gln, Pro or Lys); Xaa
at res.88 = (Asn, Asp, Ala, Glu, Gly or Lys); Xaa at
res.89 = (Met or Ala); Xaa at res.90 = (Val, Ile, Ala,
Thr, Ser or Lys); Xaa at res.91 = (Val or Ala); Xaa at
res.92 = (Arg, Lys, Gln, Asp, Glu, Val, Ala, Ser or
Thr); Xaa at res.93 = (Ala, Ser, Glu, Gly, Arg or Thr);
Xaa at res.95 = (Gly, Ala or Thr); Xaa at res.97 = (His,
Arg, Gly, Leu or Ser). Further, after res.53 in rBMP3b
and mGDF-10 there is an Ile; after res.54 in GDF-1 there
is a T; after res.54 in BMP3 there is a V; after res.78
in BMP-8 and Dorsalin there is a G; after res.37 in
hGDF-1 there is Pro, Gly, Gly, Pro.

[0071]   Generic Sequence 10 (SEQ ID NO: 8) includes
all of Generic Sequence 9 (SEQ ID NO: 7) and in addition
includes the following sequence (SEQ ID NO: 9) at its
N-terminus:

SEQ ID NO: 9

Cys	Xaa	Xaa	Xaa	Xaa
1				5

Accordingly, beginning with residue 6, each "Xaa" in
Generic Sequence 10 is a specified amino acid defined as
for Generic Sequence 9, with the distinction that each
residue number described for Generic Sequence 9 is
shifted by five in Generic Sequence 10. Thus, "Xaa at
res.1 = (Tyr, Phe, His, Arg, Thr, Lys, Gln, Val or Glu)"
in Generic Sequence 9 refers to Xaa at res.6 in Generic
Sequence 10. In Generic Sequence 10, Xaa at res.2 =
(Lys, Arg, Gln, Ser, His, Glu, Ala, or Cys); Xaa at
res.3 = (Lys, Arg, Met, Lys, Thr, Leu, Tyr, or Ala); Xaa

at res.4 = (His, Gln, Arg, Lys, Thr, Leu, Val, Pro, or Tyr); and Xaa at res.5 = (Gln, Thr, His, Arg, Pro, Ser, Ala, Gln, Asn, Tyr, Lys, Asp, or Leu).

[0072]   As noted above, certain currently preferred bone morphogenic polypeptide sequences useful in this invention have greater than 60% identity, preferably greater than 65% identity, with the amino acid sequence defining the preferred reference sequence of hOP-1. These particularly preferred sequences include allelic and phylogenetic counterpart variants of the OP-1 and OP-2 proteins, including the Drosophila 60A protein. Accordingly, in certain particularly preferred embodiments, useful BMPs include active proteins comprising pairs of polypeptide chains within the generic amino acid sequence herein referred to as "OPX" (SEQ ID NO: 4), which defines the seven cysteine skeleton and accommodates the homologies between several identified variants of OP-1 and OP-2. As described therein, each Xaa at a given position independently is selected from the residues occurring at the corresponding position in the C-terminal sequence of mouse or human OP-1 or OP-2.

SEQ ID NO: 4

```
Cys Xaa Xaa His Glu Leu Tyr Val Ser Phe Xaa Asp Leu Gly Trp Xaa Asp Trp
1           5                   10                  15
Xaa Ile Ala Pro Xaa Gly Tyr Xaa Ala Tyr Tyr Cys Glu Gly Glu Cys Xaa Phe Pro
    20              25                  30                  35
Leu Xaa Ser Xaa Met Asn Ala Thr Asn His Ala Ile Xaa Gln Xaa Leu Val His Xaa
    40              45                  50                  55
Xaa Xaa Pro Xaa Xaa Val Pro Lys Xaa Cys Cys Ala Pro Thr Xaa Leu Xaa Ala
        60              65              70
Xaa Ser Val Leu Tyr Xaa Asp Xaa Ser Xaa Asn Val Ile Leu Xaa Lys Xaa Arg
75              80              85              90
Asn Met Val Val Xaa Ala Cys Gly Cys His
        95              100
```

wherein Xaa at res.2 = (Lys or Arg); Xaa at res.3 = (Lys
or Arg); Xaa at res.11 = (Arg or Gln); Xaa at res.16 =
(Gln or Leu); Xaa at res.19 = (Ile or Val); Xaa at

5   res.23 = (Glu or Gln); Xaa at res.26 = (Ala or Ser); Xaa
at res.35 = (Ala or Ser); Xaa at res.39 = (Asn or Asp);
Xaa at res.41 = (Tyr or Cys); Xaa at res.50 = (Val or
Leu); Xaa at res.52 = (Ser or Thr); Xaa at res.56 = (Phe
or Leu); Xaa at res.57 = (Ile or Met); Xaa at res.58 =

10   (Asn or Lys); Xaa at res.60 = (Glu, Asp or Asn); Xaa at
res.61 = (Thr, Ala or Val); Xaa at res.65 = (Pro or
Ala); Xaa at res.71 = (Gln or Lys); Xaa at res.73 = (Asn
or Ser); Xaa at res.75 = (Ile or Thr); Xaa at res.80 =
(Phe or Tyr); Xaa at res.82 = (Asp or Ser); Xaa at

15   res.84 = (Ser or Asn); Xaa at res.89 = (Lys or Arg); Xaa
at res.91 = (Tyr or His); and Xaa at res.97 = (Arg or
Lys).

[0073]   In still another preferred embodiment, useful
BMPs have polypeptide chains with amino acid sequences

20   comprising a sequence encoded by a nucleic acid that
hybridizes, under low, medium or high stringency
hybridization conditions, to DNA or RNA encoding
reference BMP sequences, e.g., C-terminal sequences
defining the conserved seven cysteine domains of OP-1,

25   OP-2, BMP-2, BMP-4, BMP-5, BMP-6, 60A, GDF-5, GDF-6,
GDF-7 and the like. As used herein, high stringent
hybridization conditions are defined as hybridization
according to known techniques in 40% formamide, 5 X
SSPE, 5 X Denhardt's Solution, and 0.1% SDS at 37°C

30   overnight, and washing in 0.1 X SSPE, 0.1% SDS at 50°C.
Standard stringent conditions are well characterized in
commercially available, standard molecular cloning
texts. See, for example, *Molecular Cloning A Laboratory*

Manual, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis
(Cold Spring Harbor Laboratory Press: 1989); *DNA
Cloning*, Volumes I and II (D.N. Glover ed., 1985);
Oligonucleotide Synthesis (M.J. Gait ed., 1984): *Nucleic
Acid Hybridization* (B. D. Hames & S.J. Higgins eds.
1984); and B. Perbal, *A Practical Guide To Molecular
Cloning* (1984), the disclosures of which are
incorporated herein by reference.

[0074]   As noted above, proteins useful in the present
invention generally are dimeric proteins comprising a
folded pair of the above polypeptides. In some
embodiments, the pair of polypeptides are not disulfide
bonded. In some embodiments the pair of polypeptides
are disulfide bonded. Such disulfide bonded BMPs are
inactive when reduced, but are active as oxidized
homodimers and when oxidized in combination with others
of this invention to produce heterodimers. Thus,
members of a folded pair of bone morphogenic
polypeptides in a morphogenically active protein can be
selected independently from any of the specific
polypeptides mentioned above.

[0075]   The BMPs useful in the materials and methods
of this invention include proteins comprising any of the
polypeptide chains described above, whether isolated
from naturally-occurring sources, or produced by
recombinant DNA or other synthetic techniques, and
includes allelic and phylogenetic counterpart variants
of these proteins, as well as muteins thereof, and
various truncated and fusion constructs. Deletion or
addition mutants also are envisioned to be active,
including those which may alter the conserved C-terminal
six or seven cysteine domain, provided that the
alteration does not functionally disrupt the

relationship of these cysteines in the folded structure.
Accordingly, such active forms are considered the
equivalent of the specifically described constructs
disclosed herein. The proteins may include forms having

5   varying glycosylation patterns, varying N-termini, a
family of related proteins having regions of amino acid
sequence homology, and active truncated or mutated forms
of native or biosynthetic proteins, produced by
expression of recombinant DNA in host cells.

10   [0076]   The BMPs contemplated herein can be expressed
from intact or truncated cDNA or from synthetic DNAs in
prokaryotic or eukaryotic host cells, and purified,
cleaved, refolded, and dimerized to form morphogenically
active compositions. Alternatively, cells expressing

15   recombinant may be used in the methods of this
invention. Currently preferred host cells include,
without limitation, prokaryotes including *E. coli* or
eukaryotes including yeast, or mammalian cells, such as
CHO, COS or BSC cells. One of ordinary skill in the art

20   will appreciate that other host cells can be used to
advantage. Detailed descriptions of the bone
morphogenic proteins useful in the practice of this
invention, including how to make, use and test them for
osteogenic activity, are disclosed in numerous

25   publications, including U.S. Patent Nos. 5,266,683 and
5,011,691, the disclosures of which are incorporated by
reference herein.

[0077]   Thus, in view of this disclosure and the
knowledge available in the art, skilled genetic

30   engineers can isolate genes from cDNA or genomic
libraries of various different biological species, which
encode appropriate amino acid sequences, or construct
DNAs from oligonucleotides, and then can express them in

various types of host cells, including both prokaryotes and eukaryotes, to produce large quantities of active proteins.

Serine/Threonine Kinase Receptors

5   [0078]   TGF-β superfamily members elicit their cellular responses through formation of heteromeric complexes of specific type I and type II serine/threonine kinase receptors. To date five type II receptors and seven type I receptors (also termed

10   activin receptor-like kinases (ALKs) have been identified (See e.g., Derynck et al., Biochem. Biophys. Acta, 1333, pp. F105-F150 (1997); Massague, Annu. Rev. Biochem., 67, pp. 753-791 (1998)). The type II receptors are kinases and are constitutively active.

15   Upon ligand-mediated heteromeric complex formation, the type II receptor phosphorylates particular serine and threonine residues in the type I receptor juxtamembrane region, thereby activating the type I receptor.

       [0079]   ALK-1 was identified as an endothelial

20   specific TGF-β type I receptor (see e.g., Oh et al., Proc. Natl. Acad. Sci. U.S.A., 97, pp. 2626-2631 (2000); see also, Lux et al., J. Biol. Chem., 274, 9984-9992 (1999); US patent 5,968,752). ALK-2 was identified as a type I receptor for activin, TGF-β and BMPs (see, e.g.,

25   Attisano et al., Cell, 75, pp. 671-680 (1993); Miettinen et al., J. Cell Biol., 127, pp. 2021-2036 (1994); ten Dijke et al., Science 264, 101-104 (1994); Macias-Silva et al., J. Cell Biol., 273, pp. 25628-25636 (1998); US Patent 6,271,365). ALK-4 and ALK-5 were identified as

30   activin and TGF-β type I receptors and ALK-3 and ALK-6 were identified as BMP type I receptors (see, e.g., Oh et al., *supra* and Lux et al., *supra;* US Patents 6,271,365 and 6,207,814). ALK-7 was identified as the

type I receptor for Nodal (see, e.g., Reissman et al.,
Genes Dev., 15, pp. 2010-22 (2001); US patent
5,891,638).

[0080]   In some embodiments of the invention, type II

5   receptors are used. In some embodiments of the
invention, type I receptors are used. In yet other
embodiments of the invention, both type I and type II
receptors are used. In some embodiments, the type I
receptor is selected from the group consisting of ALK-1,

10   ALK-2, ALK-3, ALK-4, ALK-5, ALK-6, ALK-7, amino acid
sequence variants and homologs thereof, including
species homologs thereof and fragments thereof. In a
preferred embodiment, the type I receptor is ALK-2, ALK-
3 or ALK-6. In some embodiments, the type I and type II

15   receptors are recombinant.

[0081]   Publications disclosing these sequences as
well as their chemical and physical properties include:
ALK-1 (US patent 5,968,752); ALK-2, ALK-4 and ALK-5 (US
Patent 6,271,365); ALK-3 and ALK-6 (US Patent

20   6,207,814); ALK-7 (US patents 5,891,638, 5,614,609 and
5,789,565). These publications are incorporated herein
by reference.

[0082]   The type I and type II receptors contemplated
herein can be expressed from intact or truncated cDNA or

25   from synthetic DNAs in prokaryotic or eukaryotic host
cells (see discussion of protein expression, *infra*).

[0083]   Thus, in view of this disclosure and the
knowledge available in the art, skilled genetic
engineers can express these receptors in various types

30   of host cells, including both prokaryotes and
eukaryotes.

Smads

[0084]   The Smad family of proteins can be divided
into three subfamilies: R-Smads, Co-Smads and I-Smads.
The subfamily of R-Smads can be divided into two groups:
BMP-Smads and TGF-β/activin-Smads. Smad1, Smad5, and
Smad8 are phosphorylated by ALK-1, ALK-2, ALK-3 and ALK-
6, and Smad2 and Smad3 are activated by ALK-5 and ALK-4,
respectively. Smad2 and Smad3 are also activated by
ALK-7 (see e.g., Derynck et al., Biochim. Biophys. Acta,
1333, pp. F105-F150 (1997), Massague, Annu. Rev.
Biochem., 67, 753-792 (1998); Itoh et al., Eur. J.
Biochem., 267, 6954-6967 (2000)). The phosporylated R-
Smads form heteromeric complexes with Co-Smads. To date
only one Co-Smad has been identified: Smad4. I-Smads,
i.e., Smad6 and Smad7 inhibit TGF-β family signaling by
preventing the activation of R-Smads and Co-Smads (see,
e.g., Itoh et al., *supra*).

[0085]   In some embodiments, the Smads used in the
methods of this invention are selected from the group
consisting of Smad1, Smad2, Smad3, Smad5, Smad8, amino
acid sequence variants and homologs thereof, including
species homologs thereof and fragments thereof. In a
preferred embodiment, the Smad is Smad5. In another
embodiments, the Smad is recombinant.

[0086]   The sequences for Smads are included in the
following publications or are readily available to the
skilled worker from GenBank: Smad1 (rat: GenBank
Accession No. AF067727; SEQ ID NO: 12 and 13); Smad2
(mouse: GenBank Accession No. NM_010754; SEQ ID NO: 14
and 15), Smad3 (human: GenBank Accession No. NM_005902;
SEQ ID NO: 16 and 17), Smad4 (mouse: Genbank Accession
No. NM_008540; human: GenBank Accession No. NM_005359;
SEQ ID NO: 18 and 19), Smad5 (rat: GenBank Accession No.

NM_021692; SEQ ID NO: 20 and 21), Smad6 (US patents
6,534,476 and 6,270,994; human: GenBank Accession No.
NM_005585; SEQ ID NO: 22 and 23), Smad7 (US patents
6,020,464 and 6,251,628; human: GenBank Accession No.
5   NM_005904; SEQ ID NO: 24 and 25), and Smad8 (rat:
GenBank Accession No. AF012347; SEQ ID NO: 26 and 27).
These publications and GenBank Accesion numbers are
incorporated herein by reference.

[0087]   The Smads contemplated herein can be expressed
10   from intact or truncated cDNA or from synthetic DNAs in
prokaryotic or eukaryotic host cells (see discussion of
protein expression, *infra*).

[0088]   Thus, in view of this disclosure and the
knowledge available in the art, skilled genetic
15   engineers can express these receptors in various types
of host cells, including both prokaryotes and eukaryotes
(*e.g.*, progenitor cells).

Production or expression of BMPs, serine/threonine
kinase receptors and Smads

20   [0089]   The BMPs, serine/threonine kinase receptors
and Smads according to this invention may be derived
from a variety of sources. They may be isolated from
natural sources, or may be produced by expressing an
appropriate recombinant DNA molecule in a host cell. In
25   addition, the BMPs, serine/threonine kinase receptors
and Smads of this invention may be derived synthetically
and synthetic proteins may optionally be expressed from
a recombinant DNA molecule in a host cell.

1.   Naturally-derived proteins

30   [0090]   In one embodiment of this invention, the BMPs,
serine/threonine kinase receptors and Smads are isolated
from natural sources. BMPs, serine/threonine kinase

receptors and Smads may be purified from tissue sources,
preferably mammalian tissue sources, using conventional
physical and chemical separation techniques well known
to those of skill in the art.

5   2.   Recombinantly-expressed proteins

[0091]   In another embodiment of this invention, the
Smads, BMPs and serine/threonine kinase receptors and
are produced by the expression of an appropriate
recombinant DNA molecule in a host cell. The DNA and
10   amino acid sequences of Smads, BMPs and serine/threonine
kinase receptors have been reported, and methods for
their recombinant production are published and otherwise
known to those of skill in the art. For a general
discussion of cloning and recombinant DNA technology,
15   see Ausubel et al., *supra*; see also Watson et al.,
Recombinant DNA, 2d ed. 1992 (W.H. Freeman and Co., New
York).

[0092]   For cloning and expressing Smads, BMPs and
serine/threonine kinase receptors, standard recombinant
20   DNA techniques may be used. With the DNA sequence
available, a DNA fragment encoding any of these proteins
be inserted into an expression vector selected to work
in conjunction with a desired host expression system.
The DNA fragment is cloned into the vector with the
25   proper transcription control elements. In some
embodiments, the expression of the desired protein may
be constitutive. In some embodiments, the expression of
the desired protein is under the control of an inducible
promoter.

30   *Vectors*

[0093]   In some embodiments, the invention provides
vectors comprising the nucleic acids encoding Smads,
serine/threonine kinase receptors and/or BMPs. The

choice of vector and expression control sequences to which the nucleic acids of this invention are operably linked depends on the functional properties desired, e.g., protein expression, and the host cell to be transformed.

[0094] Expression control elements useful for regulating the expression of an operably linked coding sequence are known in the art. Examples include, but are not limited to, inducible promoters, constitutive promoters, secretion signals, and other regulatory elements. When an inducible promoter is used, it can be controlled, e.g., by a change in nutrient status (e.g. concentration of growth factors or BMPs), or a change in temperature, in the host cell medium.

[0095] An appropriate vector is selected according to the host system selected. Useful vectors include but are not limited to plasmids, cosmids, bacteriophage, insect and animal viral vectors, including retroviruses, and other single and double-stranded DNA viruses.

[0096] In some embodiments, it may be preferable to recombinantly produce a mammalian protein for therapeutic uses in mammalian cell culture systems in order to produce a protein whose structure resembles more closely that of the natural material. Recombinant protein production in mammalian cells requires the establishment of appropriate cells and cell lines that are easy to transfect, are capable of stably maintaining foreign DNA with an unrearranged sequence, and which have the necessary cellular components for efficient transcription, translation, post-translational modification and secretion of the protein. In addition, a suitable vector carrying the gene of interest is necessary.

[0097]   DNA vector design for transfection into
mammalian cells should include appropriate sequences to
promote expression of the gene of interest, including:
appropriate transcription initiation, termination and
enhancer sequences; efficient RNA processing signals
such as splicing and polyadenylation signals; sequences
that stabilize cytoplasmic mRNA; sequences that enhance
translation efficiency (i.e., Kozak consensus sequence);
sequences that enhance protein stability; and when
desired, sequences that enhance protein secretion.

[0098]   Preferred DNA vectors also include a marker
gene and means for amplifying the copy number of the
gene of interest.   DNA vectors may also comprise
stabilizing sequences (e.g., ori- or ARS-like sequences
and telomere-like sequences), or may alternatively be
designed to favor directed or non-directed integration
into the host cell genome.

[0099]   Substantial progress in the development of
mammalian cell expression systems has been made in the
last decade and many aspects of the system are well
characterized.   A detailed review of the production of
foreign proteins in mammalian cells, including useful
cells, protein expression-promoting sequences, marker
genes, and gene amplification methods, is disclosed in
M. M. Bendig, *Genetic Engineering*, 7, pp. 91-127 (1988).

[0100]   Particular details of the transfection,
expression and purification of recombinant proteins are
well documented and are understood by those of skill in
the art.   Further details on the various technical
aspects of each of the steps used in recombinant
production of foreign genes in mammalian cell expression
systems can be found in a number of texts and laboratory
manuals in the art.   See, e.g., F. M. Ausubel et al.,

ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York (1989).

[0101]   Briefly, among the best characterized transcription promoters useful for expressing a foreign gene in a particular mammalian cell are the SV40 early promoter, the adenovirus major late promoter (AdMLP), the mouse metallothionein-I promoter (mMT-I), the Rous sarcoma virus (RSV) long terminal repeat (LTR), the mouse mammary tumor virus long terminal repeat (MMTV-LTR), and the human cytomegalovirus major intermediate-early promoter (hCMV). The DNA sequences for all of these promoters are known in the art and are available commercially.

[0102]   One method of gene amplification in mammalian cell systems is the use of the selectable dihydrofolate reductase (DHFR) gene in a dhfr- cell line. Generally, the DHFR gene is provided on the vector carrying the gene of interest, and addition of increasing concentrations of the cytotoxic drug methotrexate (MTX) leads to amplification of the DHFR gene copy number, as well as that of the physically-associated gene of interest. DHFR as a selectable, amplifiable marker gene in transfected chinese hamster ovary cell lines (CHO cells) is particularly well characterized in the art. Other useful amplifiable marker genes include the adenosine deaminase (ADA) and glutamine synthetase (GS) genes.

[0103]   In one expression system, gene amplification is further enhanced by modifying marker gene expression regulatory sequences (e.g., enhancer, promoter, and transcription or translation initiation sequences) to reduce the levels of marker protein produced. Lowering the level of DHFR transcription increases the DHFR gene

copy number (and the physically-associated gene) to
enable the transfected cell to adapt to growth in even
low levels of methotrexate (e.g., 0.1 μM MTX). As will
be appreciated by those skilled in the art, other useful
weak promoters, different from those disclosed and
preferred herein, can be constructed using standard
vector construction methodologies. In addition, other,
different regulatory sequences also can be modified to
achieve the same effect.

[0104]   Another gene amplification scheme relies on
the temperature sensitivity (ts) of BSC40-tsA58 cells
transfected with an SV40 vector. Temperature reduction
to 33 °C stabilizes the temperature sensitive SV40 T
antigen, which leads to the excision and amplification
of the integrated transfected vector DNA thereby
amplifying the physically associated gene of interest.

[0105]   Eukaryotic cell expression vectors are known
in the art and are commercially available. Typically,
such vectors contain convenient restriction sites for
insertion of the desired DNA segment.

[0106]   Eukaryotic cell expression vectors may include
a selectable marker, e.g., a drug resistance gene. The
neomycin phosphotransferase (neo) gene (Southern et al.,
1982, J. Mol. Anal. Genet. 1:327-341) is an example of
such a gene.

[0107]   To express the desired proteins of this
invention, DNAs encoding the proteins (Smads,
serine/threonine kinase receptors and/or BMPs are
inserted into expression vectors such as plasmids,
retroviruses, cosmids, YACs, EBV-derived episomes, and
the like. The expression vector and expression control
sequences are chosen to be compatible with the
expression host cell used. In some embodiments, Smad,

serine/threonine kinase receptors and BMP nucleic acids
can be inserted into separate vectors. In some
embodiments, the Smad, serine/threonine kinase receptor
and BMP nucleic acids are inserted into the same
expression vector. In some embodiments the Smad and
serine/threonine kinase receptor nucleic acids are
inserted into the same vector. In some embodiments, the
Smad and BMP nucleic acids are inserted into the same
vector. Alternatively, any combination of Smad, BMP
and/or serine/threonine kinase receptor are inserted
into the same vector.

[0108]   A convenient vector is one that encodes a
functionally complete protein. To the extent secretion
of a desired protein is required, the recombinant
expression vector can also encode a signal peptide that
facilitates secretion of the desired protein from a host
cell.

[0109]   Nucleic acid molecules encoding Smads,
serine/threonine kinase receptors and/or BMPs, and
vectors comprising these nucleic acid molecules, can be
used for transformation of a suitable host cell.
Transformation can be by any suitable method. Methods
for introduction of exogenous DNA into mammalian cells
are well known in the art and include dextran-mediated
transfection, calcium phosphate precipitation,
polybrene-mediated transfection, protoplast fusion,
electroporation, encapsulation of the polynucleotide(s)
in liposomes, and direct microinjection of the DNA into
nuclei. In addition, nucleic acid molecules may be
introduced into mammalian cells by viral vectors.

[0110]   Transformation of host cells can be
accomplished by conventional methods suited to the
vector and host cell employed. For transformation of

prokaryotic host cells, electroporation and salt treatment methods can be employed (Cohen et al., 1972, Proc. Natl. Acad. Sci. USA 69:2110-2114). For transformation of vertebrate cells, electroporation, cationic lipid or salt treatment methods can be employed. See, e.g., Graham et al., 1973, Virology 52:456-467; Wigler et al., 1979, Proc. Natl. Acad. Sci. USA 76:1373-1376f.

Host Cells

[0111]   Host cells can be prokaryotic or eukaryotic. Useful host cells include but are not limited to bacteria such as *E. coli*, yeasts such as *Saccharomyces* and *Picia*, insect-baculovirus cell system, and primary, transformed or immortalized eukaryotic cells in culture. Preferred eukaryotic host cells include, but are not limited to, yeast and mammalian cells, e.g., Chinese hamster ovary (CHO) cell, NIH Swiss mouse embryo cells NIH-3T3, baby hamster kidney cells (BHK), C2C12 cells and BSC cells. Other useful eukaryotic cells include osteoprogenitor cells, cartilage progenitor cells, tendon progenitor cells, ligament progenitor cells and neural progenitor cells.

[0112]   The methodology disclosed herein includes the use of COS cells for the rapid evaluation of vector construction and gene expression, and the use of established cell lines for long term protein production.

[0113]   The choice of cells/cell lines is also important and depends on the needs of the skilled practitioner. Monkey kidney cells (COS) provide high levels of transient gene expression providing a useful means for rapidly testing vector construction and the expression of cloned genes. COS cells are transfected

with a simian virus 40 (SV40) vector carrying the gene
of interest. The transfected COS cells eventually die,
thus preventing the long term production of the desired
protein product. However, transient expression does not

5   require the time consuming process required for the
development of stable cell lines.

[0114]   CHO cells are capable of successfully
expressing a wide variety of proteins from a broad range
of cell types. Thus, while the glycosylation pattern on

10   a recombinant protein produced in a mammalian cell
expression system may not be identical to the natural
protein, the differences in oligosaccharide side chains
are often not essential for biological activity of the
expressed protein.

15   [0115]   The DHFR gene also may be used as part of a
gene amplification scheme for CHO cells. Another gene
amplification scheme relies on the temperature
sensitivity (ts) of BSC40-tsA58 cells transfected with
an SV40 vector. Temperature reduction to 33 °C

20   stabilizes the ts SV40 T antigen which leads to the
excision and amplification of the integrated transfected
vector DNA, thereby also amplifying the associated gene
of interest.

[0116]   Stable cell lines were established for CHO

25   cells as well as BSC40-tsA58 cells (hereinafter referred
to as "BSC cells"). The various cells, cell lines and
DNA sequences chosen for mammalian cell expression of
the Smads, serine/threonine kinase receptors and BMPs of
this invention are well characterized in the art and are

30   readily available. Other promoters, selectable markers,
gene amplification methods and cells also may be used to
express the Smads, serine/threonine kinase receptors and
BMPs of this invention. Particular details of the

transfection, expression, and purification of
recombinant proteins are well documented in the art and
are understood by those having ordinary skill in the
art. Further details on the various technical aspects
5   of each of the steps used in recombinant production of
foreign genes in mammalian cell expression systems can
be found in a number of texts and laboratory manuals in
the art. See, e.g., F. M. Ausubel et al., ed., *Current
Protocols in Molecular Biology*, John Wiley & Sons, New
10   York (1989).

Progenitor cells

[0117]   The progenitor cells that are induced to
proliferate and/or differentiate in the present
invention are preferably mammalian cells. Preferred
15   progenitor cells include mammalian chondroblasts,
osteoblasts and neuroblasts, all earlier developmental
precursors thereof, and all cells that develop therefrom
(e.g., chondroblasts, pre-chondroblasts and
chondrocytes). However, any non-mammalian progenitor
20   cells are also likely to be useful in the methods of the
present invention. It is, thus, envisioned that when
schemes become available for implanting xenogeneic cells
into humans without causing adverse immunological
reactions, non-mammalian progenitor cells will be useful
25   for tissue regeneration and repair in humans.

[0118]   In some embodiments, the progenitor cells
comprise a nucleic acid encoding a Smad and optionally a
nucleic acid encoding one or more serine/threonine
kinase receptor and/or a nucleic acid encoding one or
30   more BMP. In some embodiments, the progenitor cells
comprise vectors comprising a nucleic acid encoding a
Smad and optionally a nucleic acid encoding one or more

serine/threonine kinase receptor and/or a nucleic acid
encoding one or more BMP. In some embodiments, the
nucleic acid encoding Smad, serine/threonine kinase
receptor and/or BMP are in one vector. In some

5   embodiments, the nucleic acid encoding Smad,
serine/threonine kinase receptor and/or BMP are in
different vectors. In some embodiments, the nucleic
acids are recombinant.

[0119]   In some embodiments, only type I

10 serine/threonine kinase receptors are used. In some
embodiments, only type II serine/threonine kinase
receptors are used. In other embodiments, both type I
and type II serine/threonine kinase receptors are used.
In some embodiments, more than one BMP will be

15 administered to the desired cell or tissue. In some
embodiments, two BMPS will be used. In some
embodiments, three BMPs will be used. The particular
choice of combination of BMPs and the relative
concentrations at which they are combined may be varied

20 systematically to optimize the tissue type induced at a
selected treatment site using the procedures described
herein. The relative concentrations of the BMPs either
alone or in combination that will optimally induce
tissue formation when administered to a mammal may be

25 determined empirically by the skilled practitioner using
the procedures described herein.

Gene Therapy

[0120]   The Smad, serine/threonine kinase receptor
and/or BMP proteins can be produced *in vivo* in a mammal,

30 e.g., a human patient, using a gene therapy approach for
inducing tissue formation, repairing a tissue defect or
regenerating tissue at a target locus. This involves

administration of a suitable Smad, serine/threonine
kinase receptor and/or BMP protein-encoding nucleic acid
operably linked to suitable expression control
sequences. Preferably, these sequences are incorporated

5   into a viral vector. Suitable viral vectors for such
gene therapy include adenoviral vectors, lentiviral
vectors, baculoviral vectors, Epstein Barr viral
vectors, papovaviral vectors, vaccinia viral vectors,
herpes simplex viral vectors, and adeno associated virus

10   (AAV) vectors. The viral vector can be a replication-
defective viral vector. A preferred adenoviral vector
has a deletion in its E1 gene or E3 gene. When an
adenoviral vector is used, preferably the mammal is not
exposed to a nucleic acid encoding a selectable marker

15   gene.

Formulations

[0121]   The proteins (e.g., BMPs) of the present
invention can be formulated as part of a pharmaceutical
composition. The pharmaceutical compositions provided

20   by this invention comprise at least one protein. The
compositions of this invention will be administered at
an effective dose to induce the particular type of
tissue at the treatment site selected according to the
particular clinical condition addressed. Determination

25   of a preferred pharmaceutical formulation and a
therapeutically effective dose regimen for a given
application is well within the skill of the art taking
into consideration, for example, the mode of
administration, the condition and weight of the patient,

30   the extent of the desired treatment and the tolerance of
the patient for the treatment.

[0122]   Administration of the proteins of this invention, may be accomplished using any of the conventional modes of administration.

[0123]   The pharmaceutical compositions comprising a protein of this invention may be in a variety of forms. These include, for example, solid, semi-solid and liquid dosage forms such as tablets, pills, powders, liquid solutions or suspensions, suppositories, and injectable and infusible solutions. The preferred form depends on the intended mode of administration and therapeutic application and may be selected by one skilled in the art. Modes of administration may include oral, parenteral, subcutaneous, intravenous, intralesional or topical administration. In most cases, the pharmaceutical compositions of this invention will be administered in the vicinity of the treatment site in need of tissue regeneration or repair.

[0124]   The pharmaceutical compositions comprising a protein of this invention may, for example, be placed into sterile, isotonic formulations with or without cofactors which stimulate uptake or stability. The formulation is preferably liquid, or may be lyophilized powder. For example, the BMP of this invention may be diluted with a formulation buffer comprising 5.0 mg/ml citric acid monohydrate, 2.7 mg/ml trisodium citrate, 41 mg/ml mannitol, 1 mg/ml glycine and 1 mg/ml polysorbate 20. This solution can be lyophilized, stored under refrigeration and reconstituted prior to administration with sterile Water-For-Injection (USP).

[0125]   The compositions also will preferably include conventional pharmaceutically acceptable carriers well known in the art (see for example Remington's Pharmaceutical Sciences, 16th Edition, 1980, Mac

Publishing Company). Such pharmaceutically acceptable
carriers may include other medicinal agents, carriers,
genetic carriers, adjuvants, excipients, etc., such as
human serum albumin or plasma preparations. The

5   compositions are preferably in the form of a unit dose
and will usually be administered as a dose regimen that
depends on the particular tissue treatment.

[0126]   The pharmaceutical compositions of this
invention may also be administered in conjunction with a

10   morphogenic device using, for example, microspheres,
liposomes, other microparticulate delivery systems or
sustained release formulations placed in, near, or
otherwise in communication with affected tissues or the
bloodstream bathing those tissues.

15   [0127]   Liposomes containing a protein of this
invention can be prepared by well-known methods (See,
e.g. DE 3,218,121; Epstein et al., Proc. Natl. Acad.
Sci. U.S.A., 82, pp. 3688-92 (1985); Hwang et al., Proc.
Natl. Acad. Sci. U.S.A., 77, pp. 4030-34 (1980); U.S.

20   Patent Nos. 4,485,045 and 4,544,545). Ordinarily the
liposomes are of the small (about 200-800 Angstroms)
unilamellar type in which the lipid content is greater
than about 30 mol.% cholesterol. The proportion of
cholesterol is selected to control the optimal rate of

25   BMP release.

[0128]   The proteins of this invention may also be
attached to liposomes containing other biologically
active molecules such as immunosuppressive agents,
cytokines, etc., to modulate the rate and

30   characteristics of tissue induction. Attachment of BMPs
to liposomes may be accomplished by any known cross-
linking agent such as heterobifunctional cross-linking
agents that have been widely used to couple toxins or

chemotherapeutic agents to antibodies for targeted
delivery. Conjugation to liposomes can also be
accomplished using the carbohydrate-directed cross-
linking reagent 4-(4-maleimidophenyl) butyric acid

5   hydrazide (MPBH) (Duzgunes et al., J. Cell. Biochem.
Abst. Suppl. 16E 77 (1992)).

[0129]   The following are examples which illustrate
the methods of this invention. These examples should
not be construed as limiting: the examples are included

10   for purposes of illustration and the present invention
is limited only by the claims.

Example 1 - Effect of CDMP-1 and OP-1 on Smad5 levels

[0130]   Total C2C12 cell lysates treated with solvent

15   control (lane 1), CDMP-1 (200 ng/ml), or OP-1 (100
ng/ml) were collected after 5 days. Proteins in the
lysates were resolved by SDS-PAGE, transferred to nylon
membranes, and analyzed using the anti-human Smad5
antibody (Cell Signaling Technology, Inc., Beverly, MA),

20   as the primary antibody and anti-rabbit IgG HRP-
conjugated antibody was used as the secondary antibody.
Immunoreactive bands were detected using the SuperSignal
chemiluminescent detection system (Pierce, Rockford,
IL), according to the manufacturer's instructions.

25   Representative results of two independent experiments
are shown. Western blot analyses showed that the Smad5
protein level in control C2C12 cells was hardly
detectable by Western blot analysis (Figure 1, lane 1).
CDMP-1 alone stimulated Smad5 protein expression in

30   C2C12 cells (Figure 1, lane 2). OP-1 alone stimulated
Smad5 protein expression to a higher level (Figure 1,
lane 3). The combination of CDMP-1 and OP-1
significantly stimulated Smad5 protein expression even

more (Figure 1, lane 4). The current observation that
the protein level of Smad5 was dramatically increased in
cells treated with the combination of OP-1 and CDMP-1
would support the supposition that the effect of the

5   combination of OP-1 and CDMP-1 is likely directed at the
Smad signaling pathway.

Example 2 - Co-transfection with the OP-1 Gene and the
CDMP-1 Gene

10   [0131]   Target cells will be transfected with plasmids
or viral carriers containing the OP-1 gene and the CDMP-
1 gene under an appropriate promoter. In addition,
these cells will be transfected with plasmids or viral
carriers containing the Smad5 gene. For example,

15   plasmid pW24 (10.35 kb) that contains the coding
sequence for OP-1 under the control of the CMV promoter
may be used. Similarly, plasmids containing the CMDP-1
gene (pCDMP-1) or the Smad5 gene (pSmad5) will be
constructed by replacing the OP-1 gene in the pW24

20   plasmid. Alternatively, these genes may be placed under
the control of promoters that can be induced thus
allowing control of expression at will. Additional
vectors, such as adenoviral vectors may be constructed
and tested in order to optimize and maximize expression.

25   [0132]   Target cells that have been shown capable to
become osteoblastic upon treatment with OP-1 include
osteoblastic cells such as FRC cells, and pluripotent
mesenchymal cells such as C2C12 and C3H10T1/2 cell
lines. Cells of other orthopaedic utility may also be

30   used. These include cells derived from cartilage,
tendon, ligament, and meniscus.

[0133]   Transfection studies will be carried out using
the calcium phosphate-DNA coprecipitation method or

FuGene6 (Roche Diagnostics). Briefly, cells will be

transfected with the specified plasmid DNAs (1 µg/ml) in

serum-free medium for 4-6 h. The medium will be

replaced with complete αMEM containing 10% FBS.

5   *Example 3 - Effect of OP-1, CDMP-1 and/or Smad5 on*

Alkaline Phosphatase Activity

[0134]   The effect of co-transfection of FRC cells

with pW24 and pCDMP-1 and/or pSmad5 will be examined.

For example, FRC cells will be transfected with pW24,

10   pCDMP-1 and/or pSmad5. After 48 h, total AP activity

will be measured. It is anticipated that the AP

activity in cells co-transfected with pW24, pCDMP-1

and/or pSmad5 will increase as a function of pCDMP-1

and/or pSmad5 concentration. The increase should be

15   beyond that in cells transfected with pW24 alone. The

AP activity in cells transfected with pCDMP-1 alone will

also show a lesser but significant increase compared to

the non-transfected control or cells transfected with

the empty plasmids (vectors without the OP-1, CDMP-1

20   and/or Smad5 genes). Co-transfection with pW24 and the

empty plasmid is not expected to result in an increase

in AP activity beyond that by pW24 alone. Protein

levels of OP-1, CDMP-1, and Smad5 under these conditions

will be measured by Western blot analysis. Control

25   experiments will include co-transfection of FRC cells

with the empty plasmids, i.e. vector without the OP-1,

CDMP-1 or Smad5 genes. It is expected that the AP

activity will not be elevated beyond the non-transfected

controls. The expression of additional osteoblastic

30   cell markers, such as osteocalcin (OC) and bone

sialoprotein (BSP) will also be monitored using either

Northern blot analysis or real-time PCR. Transfection

conditions for other cell types will be optimized
accordingly using art recognized methods.

Example 4 - Effect of OP-1, CDMP-1 and/or Smad5 on Mineralized Bone Nodule Formation

5   [0135]   The effect of co-transfection of FRC cells
with pW24 and pCDMP-1 or pSmad5 on mineralized bone
nodule formation will be examined. Confluent FRC cells
will be co-transfected with pW24 and pCDM-1 and/or
pSmad5 using FuGene6 using the optimal ratio of pW24 to
10   pCDMP-1 or pSmad5 as determined by the experiments
described above. Cells will be cultured in complete
αMEM containing 5% FBS, ascorbic acid, and β-glycerol
phosphate in the presence of 250 μg/ml of Neomycin.
Media will be changed every 3 days. Progress of nodule
15   formation will be monitored periodically and the images
will be captured using an Olympus CK2 inverted
microscope equipped with a CCD camera. At the
termination of the experiments, cultures will be stained
by Alizarin Red-S staining to assess the extent of
20   formation of mineralized bone nodules.

Example 5 - In vivo Expression of OP-1, CDMP-1 and Smad5

[0136]   In vivo studies will be conducted using two
experimental approaches: (i) Direct injection of OP-1
25   expressing vectors together with CDMP-1 and/or Smad5-
expressing vectors into muscles of mice, and (ii)
injection of transfected cells into muscles.

[0137]   For direct injection experiments, nude mice
will be injected with vectors expressing OP-1, CDMP-1
30   and/or Smad5 (pW24, pCDMP-1 and/or pSmad5, respectively)
with a 27-gauge needle subcutaneously into a male
homozygous nude mouse. Standard aseptic techniques will
be used in all manipulations. To determine in vivo

osteogenic dose response of the vectors, eight mice will
be used. Each mouse will be injected with 0.1 - 10
mg/ml vectors in 100 μl each. Body weight and growth at
the site of injection will be followed daily via in-life

5   measurement of the mass. The cross-sectional area of
the mass will be measured with a vernier caliper. The
size of the mass will be calculated using the formula:
length/2 x width/2 x Л. The mass and the body weight
will be plotted as a function of time following

10   injection. The animals will be monitored for 49 days.
At necropsy, the mass at the site of injection will be
collected, fixed, stained with hematoxylin and eosin,
and subjected to histological analysis. Controls will
include mice injected with individual pW24, pCDMP-1

15   and/or pSmad5 alone. It is anticipated that the bone
mass in mice injected with the combination of the pW24
and pCDMP-1, or pW24 plus pSmad5 will be greater than
that injected with individual vector alone.

[0138]   For experiments using injection of cells,

20   similar experiments as described above will be conducted
except that animals will be injected with cells co-
transfected with vectors carrying the OP-1, CDMP-1,
and/or Smad5 genes. Accordingly, cells will be grown to
mid-log phase and transfected with a combination of

25   vectors expressing OP-1, CDMP-1 and/or Smad5 as
described above using the optimal ratio of the two
vectors. Cells will be removed from the culturing
dishes by trypsin-EDTA digestion. Trypsin will be
inactivated by serum (10%) and removed by repeated

30   washings with HBSS. Cells will be suspended in a
minimal volume of HBSS and injected with a 27-gauge
needle subcutaneously into the flank of a male
homozygous nude mouse. Standard aseptic techniques will

be used in all manipulations. Eight nude mice will be
injected with 10^6 cells in 100 μl each. Outcome
measurements as described above will be conducted. It
is anticipated that the bone mass in mice injected with
5   cells transfected with the combination of the pW24 and
pCDMP-1, or pW24 plus pSmad5 will be greater than that
injected with cells transfected with individual vector
alone.

Example 6 - Gene Therapy In Patients Using Transfected
10 *Cells*

[0139]   For cell therapeutics with tranfected genes,
appropriate cells will be transfected *in vitro* with DNA
vectors carrying the OP-1 gene, the CDMP-1 gene, and/or
the Smad5 gene and optionally a serine/threonine kinase
15 receptor. Appropriate cells include osteoblasts or
osteoblastic cell progenitors for the repair of bone
defects. For repair of cartilage regeneration, cells of
chondrocyte origin or chondrogenitor cells will be
appropriate. Similarly, for the regeneration of tendons
20 or ligaments, the appropriate cells include progenitor
cells of tendon or ligament origin. The transfected
cells will be cultured to allow expression of the
transfected gene(s). The cells will then be injected or
implanted into a defect site in a patient. The defect
25 site may be in bone, cartilage, tendon, ligament or
neural tissue. The number of cells injected or
implanted into the defect will depend on the size of the
defect. Exemplary DNA vectors will be pW24, pCDMP-1, or
pSmad5 as described previously.

30 *Example 7 - Gene Therapy In Patients Using Transfected*
Cells

[0140]   For directed gene therapy, a combination of
vectors as described above carrying the OP-1 gene, the

cDMP-1 gene, the Smad5 gene and/or a serine/threonine
kinase will be injected into the defect site in a
patient. The genes encoding each of the proteins may be
placed in the same vector or in separate vectors.

5   **Example 8 - Monitoring Effects of Gene Therapy in**
     Patients

     [0141]   The repair site will be monitored
     radiographically every two weeks for a minimum of two
     years. It is anticipated that the defect site which
10   receives the combination of OP-1 + CDMP-1 + Smad or OP-1
     + Smad5 (delivered by either of the methods described in
     Examples 6 and 7) will exhibit a faster rate of repair
     than that receives OP-1 alone.

     [0142]   In case of cartilage and tendon/ligament
15   repair, delivery of pCDMP-1 alone to a defect site will
     induce tissue formation. However, delivery of OP-1 +
     CDMP-1 to a defect site should exhibit a faster rate of
     repair than delivery of CDMP-1 or Smad5 alone. In all
     cases, the treated sites should exhibit regeneration
20   whereas those treated with vehicle should not.

We Claim:

1.   A method of inducing the expression of a Smad in a cell or tissue comprising contacting the cell or tissue capable of expressing the Smad with a bone morphogenic protein.

2.   The method according to claim 1, wherein the cell or tissue is contacted with two bone morphogenic proteins.

3.   The method according to claim 1 or 2, wherein each bone morphogenic protein is independently selected from the group consisting of OP-1 (BMP-7), OP-2, OP-3, COP-1, COP-3, COP-4, COP-5, COP-7, COP-16, BMP-2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, BMP-9, BMP-10, BMP-11, CDMP-3 (BMP-12), CDMP-2 (BMP-13), CDMP-1 (BMP-14), BMP-15, BMP-16, BMP-17, BMP-18, GDF-1, GDF-2, GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11, GDF-12, MP121, dorsalin-1, DPP, Vg-1, Vgr-1, 60A protein, NODAL, UNIVIN, SCREW, ADMP, and NEURAL.

4.   The method according to claim 1, wherein the bone morphogenic protein is OP-1.

5.   The method according to claim 1, wherein the bone morphogenic protein is CDMP-1 or GDF-5.

6.   The method according to claim 2, wherein the first bone morphogenic protein is OP-1 and the second bone morphogenic protein is selected from the group consisting of CDMP-1, and GDF-5.

7.   The method according to claim 1 or 2, wherein the Smad is selected from the group consisting of Smad1, Smad2, Smad3, Smad5 and Smad8.

8.   The method according to claim 7, wherein the Smad is Smad5.

9.   The method according to claim 1, wherein the Smad is a recombinant Smad.

10.   The method according to claim 1 or 2, wherein the cell or tissue is further capable of expressing a serine/threonine kinase receptor.

11.   The method according to claim 10, wherein the serine/threonine kinase receptor is a type I receptor.

12.   The method according to claim 10, wherein the serine/threonine kinase receptor is a type II receptor.

13.   The method according to claim 10, wherein the cell or tissue is further capable of expressing both type I and type II serine/threonine kinase receptor.

14.   The method according to claim 11 or 13, wherein the type I receptor is selected from the group consisting of ALK-1, ALK-2, ALK-3, ALK-4, ALK-5, ALK-6, and ALK-7.

15.   The method according to claim 10 wherein the serine/threonine kinase receptor is a recombinant serine/threonine kinase receptor.

16. The method according to claim 1 or 2 wherein the tissue is selected from the group consisting of bone, cartilage, tendon, ligament and neural tissue.

17. The method according to claim 1 or 2 wherein the cell is a progenitor cell.

18. The method according to claim 17, wherein the progenitor cell is selected from the group consisting of an osteoprogenitor cell, a cartilage progenitor cell, a ligament progenitor cell, a tendon progenitor cell, and a neural progenitor cell.

19. A method of inducing tissue formation at a target locus in a mammal comprising the step of administering to the target locus a nucleic acid encoding a Smad.

20. A method of inducing tissue formation at a target locus in a mammal comprising the step of administering to the target locus a vector comprising a nucleic acid encoding a Smad operably linked to an expression control sequence.

21. A method of inducing tissue formation at a target locus in a mammal comprising the step of administering to the target locus a cell comprising a vector comprising a nucleic acid encoding a Smad operably linked to an expression control sequence.

22. A method of repairing a tissue defect or regenerating tissue at a target locus in a mammal comprising the step of administering to the target locus a nucleic acid encoding a Smad.

23.   A method of repairing a tissue defect or regenerating tissue at a target locus in a mammal comprising the step of administering to the target locus a vector comprising a nucleic acid encoding a Smad operably linked to an expression control sequence.

24.   A method of repairing a tissue defect or regenerating tissue at a target locus in a mammal comprising the step of administering to the target locus a cell comprising a vector comprising a nucleic acid encoding a Smad operably linked to an expression control sequence.

25.   The method according to any one of claims 20, 21, 23 or 24, wherein the expression control sequence comprises a constitutive promoter.

26.   The method according to claim 20, 21, 23 or 24, wherein the expression control sequence comprises an inducible promoter.

27.   The method according to any one of claims 19-24, wherein the Smad is selected from the group consisting of Smad1, Smad2, Smad3, Smad5 and Smad8.

28.   The method according to claim 27, wherein the Smad is Smad5.

29.   The method according to any one of claims 19-28, wherein the Smad is recombinant Smad.

30.   The method according to any one of claims 19-24 further comprising the step of

administering to the target locus a nucleic acid
encoding a serine/threonine kinase receptor.

31.   The method according to any one of
claims 19-24 further comprising the step of
administering to the target locus a vector comprising a
nucleic acid encoding a serine/threonine kinase
receptor operably linked to an expression control
sequence.

32.   The method according to any one of
claims 19-24 further comprising the step of
administering to the target locus a cell comprising a
vector comprising a nucleic acid encoding a
serine/threonine kinase receptor operably linked to an
expression control sequence.

33.   The method according to claim 31 or 32,
wherein the expression control sequence operably linked
to the serine/threonine kinase receptor comprises a
constitutive promoter.

34.   The method according to claim 31 or 32,
wherein the expression control sequence operably linked
to the serine/threonine kinase receptor comprises an
inducible promoter.

35.   The method according to any one of
claims 33-32, wherein the serine/threonine kinase
receptor is a type I receptor.

36.   The method according to any one of
claims 33-32, wherein the serine/threonine kinase
receptor is a type II receptor.

37. The method according to any one of
claims 33-32, wherein both type I and type II
serine/threonine kinase receptors are administered.

38. The method according to any one of claim
35 or 37, wherein the type I receptor is selected from
the group consisting of ALK-1, ALK-2, ALK-3, ALK-4,
ALK-5, ALK-6, and ALK-7.

39. The method according to claim 38,
wherein the serine/threonine kinase receptor is
selected from the group consisting of ALK-2, ALK-3, and
ALK-6.

40. The method according to claim 30-32,
wherein the serine/threonine kinase receptor is a
recombinant ALK.

41. The method according to any one of
claims 19-24, further comprising the step of
administering to the target locus a bone morphogenic
protein.

42. The method according to any one of
claims 19-24, further comprising the step of
administering to the target locus a nucleic acid
encoding a bone morphogenic protein.

43. The method according to any one of
claims 19-24, further comprising the step of
administering to the target locus a vector comprising a
nucleic acid encoding a bone morphogenic protein
operably linked to an expression control sequence.

44. The method according to any one of
claims 19-24, further comprising the step of
administering to the target locus a cell comprising a
vector comprising a nucleic acid encoding a bone
morphogenic protein operably linked to an expression
control sequence.

45. The method according to any one of
claims 41-44, wherein the bone morphogenic protein is
selected from the groups consisting of OP-1 (BMP-7),
OP-2, OP-3, COP-1, COP-3, COP-4, COP-5, COP-7, COP-16,
BMP-2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, BMP-9, BMP-
10, BMP-11, CDMP-3 (BMP-12), CDMP-2 (BMP-13), CDMP-1
(BMP-14), BMP-15, BMP-16, BMP-17, BMP-18, GDF-1, GDF-2,
GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-
11, GDF-12, MP121, dorsalin-1, DPP, Vg-1, Vgr-1, 60A
protein, NODAL, UNIVIN, SCREW, ADMP, and NEURAL.

46. The method according to claim 45,
wherein the bone morphogenic protein is OP-1.

47. The method according to any one of
claims 19-24, wherein the tissue is selected from the
group consisting of bone, cartilage, tendon, ligament
and neural tissue.

48. The method according to claim 21 or 24,
wherein the cell is a progenitor cell.

49. The method according to claim 48,
wherein the progenitor cell is selected from the group
consisting of an osteoprogenitor cell, a cartilage
progenitor cell, a ligament progenitor cell, a tendon
progenitor cell, and a neural progenitor cell.

FIGURE 1

Control   CDMP-1   OP-1   OP-1+ CDMP-1

   1   2   3   4
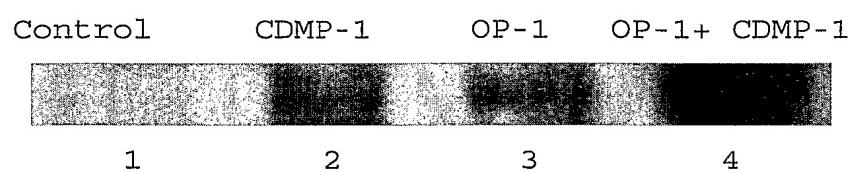
Figure 2

Plasmid map of pW24 containing OP-1 gene
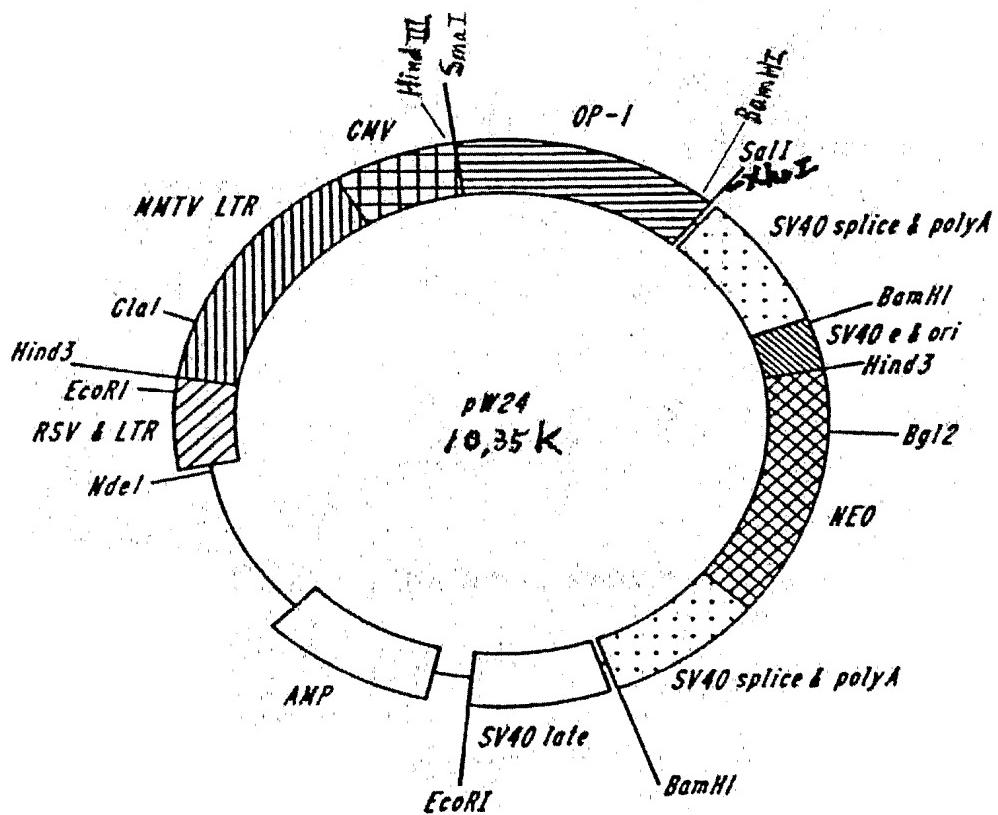
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            20   25   30

Leu Asp Asn Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser
        35   40   45

Gln Glu Arg Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu
    50   55   60

Pro His Arg Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro
65   70   75   80

Met Phe Met Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Gly Gly
            85   90   95

Gly Pro Gly Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser
            100   105   110

Thr Gln Gly Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr
            115   120   125

Asp Ala Asp Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys
        130   135   140

Glu Phe Phe His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu
145   150   155   160

Ser Lys Ile Pro Glu Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile
                165   170   175

Tyr Lys Asp Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Glu Arg Ile
            180   185   190

Ser Val Tyr Gln Val Leu Gln Glu His Leu Gly Arg Glu Ser Asp Leu
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Phe Leu Leu Asp Ser Arg Thr Leu Trp Ala Ser Glu Glu Gly Trp Leu
    210   215   220

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225   230   235   240

His Asn Leu Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser
            245   250   255

Ile Asn Pro Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn
            260   265   270

Lys Gln Pro Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Phe
        275   280   285

Arg Ser Ile Arg Ser Thr Gly Ser Lys Gln Arg Ser Gln Asn Arg Ser
    290   295   300

Lys Thr Pro Lys Asn Gln Glu Ala Leu Arg Met Ala Asn Val Ala Glu
305   310   315   320

Asn Ser Ser Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr
            325   330   335

Val Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu
        340   345   350

Gly Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn
        355   360   365

Ser Tyr Met Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His
        370   375   380

Phe Ile Asn Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln
385   390   395   400

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Val Asn Ser Val Asn Ser Lys Ile Pro Lys Ala Cys Cys Val Pro Thr
        50   55   60

Glu Leu Ser Ala Ile Ser Met Leu Tyr Leu Asp Glu Asn Glu Lys Val
65   70   75   80

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Page 3

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn His Ala Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Cys Xaa Pro
    50   55   60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Cys Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa Phe Xaa Xaa Xaa Gly Trp Xaa
1   5   10   15

Xaa Xaa Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa Ala Xaa Tyr Cys Xaa Gly
            20   25   30

Xaa Cys Xaa Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn His Ala
        35   40   45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
    50   55   60

Xaa Cys Cys Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Xaa
65   70   75   80

Xaa Xaa Xaa Xaa Xaa Val Xaa Leu Xaa Xaa Xaa Xaa Xaa Met Xaa Val
            85   90   95

Xaa Xaa Cys Xaa Cys Xaa
            100


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<220>
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specified amino acids as defined in the specification

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<400>  7

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1                   5                   10                  15


Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Gly Xaa Cys Xaa Xaa Xaa
            20                  25                  30


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Pro
    50                  55                  60


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65                  70                  75                  80


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Cys
            85                  90                  95


Xaa



<210>  8
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<220>
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<400>  8

Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Gly
```

```
                20                      25                      30


Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                      40                      45


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
    50                      55                      60


Xaa Xaa Cys Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Xaa
65                      70                      75                      80


Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            85                      90                      95


Xaa Xaa Cys Xaa Cys Xaa
            100


<210>  9
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<213>  Artificial Sequence

<220>
<223>  Consensus Sequence


<220>
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<400>  9

Cys Xaa Xaa Xaa Xaa
1               5


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<212>  DNA
<213>  Homo sapiens


<220>
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                                                        Met His Val
                                                          1
```

```
cgc tca ctg cga gct gcg gcg ccg cac agc ttc gtg gcg ctc tgg gca     105
Arg Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala Leu Trp Ala
      5                  10                  15
```

```
ccc ctg ttc ctg ctg cgc tcc gcc ctg gcc gac ttc agc ctg gac aac     153
Pro Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser Leu Asp Asn
20                  25                  30                  35
```

```
gag gtg cac tcg agc ttc atc cac cgg cgc ctc cgc agc cag gag cgg     201
Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser Gln Glu Arg
                40                  45                  50
```

```
cgg gag atg cag cgc gag atc ctc tcc att ttg ggc ttg ccc cac cgc     249
Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu Pro His Arg
                55                  60                  65
```

```
ccg cgc ccg cac ctc cag ggc aag cac aac tcg gca ccc atg ttc atg     297
Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro Met Phe Met
            70                  75                  80
```

```
ctg gac ctg tac aac gcc atg gcg gtg gag gag ggc ggc ggg ccc ggc     345
Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Gly Gly Gly Pro Gly
        85                  90                  95
```

```
ggc cag ggc ttc tcc tac ccc tac aag gcc gtc ttc agt acc cag ggc     393
Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser Thr Gln Gly
100                 105                 110                 115
```

```
ccc cct ctg gcc agc ctg caa gat agc cat ttc ctc acc gac gcc gac     441
Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr Asp Ala Asp
                120                 125                 130
```

```
atg gtc atg agc ttc gtc aac ctc gtg gaa cat gac aag gaa ttc ttc     489
Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys Glu Phe Phe
                135                 140                 145
```

```
cac cca cgc tac cac cat cga gag ttc cgg ttt gat ctt tcc aag atc     537
His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu Ser Lys Ile
                150                 155                 160
```

```
cca gaa ggg gaa gct gtc acg gca gcc gaa ttc cgg atc tac aag gac     585
Pro Glu Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Asp
                165                 170                 175
```

```
tac atc cgg gaa cgc ttc gac aat gag acg ttc cgg atc agc gtt tat     633
Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Phe Arg Ile Ser Val Tyr
180                 185                 190                 195
```

```
cag gtg ctc cag gag cac ttg ggc agg gaa tcg gat ctc ttc ctg ctc     681
Gln Val Leu Gln Glu His Leu Gly Arg Glu Ser Asp Leu Phe Leu Leu
                200                 205                 210
```

```
gac agc cgt acc ctc tgg gcc tcg gag gag ggc tgg ctg gtg ttt gac     729
Asp Ser Arg Thr Leu Trp Ala Ser Glu Glu Gly Trp Leu Val Phe Asp
                215                 220                 225
```

```
atc aca gcc acc agc aac cac tgg gtg gtc aat ccg cgg cac aac ctg      777
Ile Thr Ala Thr Ser Asn His Trp Val Val Asn Pro Arg His Asn Leu
        230                     235                 240

ggc ctg cag ctc tcg gtg gag acg ctg gat ggg cag agc atc aac ccc      825
Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser Ile Asn Pro
        245                     250                 255

aag ttg gcg ggc ctg att ggg cgg cac ggg ccc cag aac aag cag ccc      873
Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn Lys Gln Pro
260                 265                 270                 275

ttc atg gtg gct ttc ttc aag gcc acg gag gtc cac ttc cgc agc atc      921
Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Phe Arg Ser Ile
                280                 285                 290

cgg tcc acg ggg agc aaa cag cgc agc cag aac cgc tcc aag acg ccc      969
Arg Ser Thr Gly Ser Lys Gln Arg Ser Gln Asn Arg Ser Lys Thr Pro
                295                 300                 305

aag aac cag gaa gcc ctg cgg atg gcc aac gtg gca gag aac agc agc     1017
Lys Asn Gln Glu Ala Leu Arg Met Ala Asn Val Ala Glu Asn Ser Ser
        310                 315                 320

agc gac cag agg cag gcc tgt aag aag cac gag ctg tat gtc agc ttc     1065
Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr Val Ser Phe
        325                 330                 335

cga gac ctg ggc tgg cag gac tgg atc atc gcg cct gaa ggc tac gcc     1113
Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala
340                 345                 350                 355

gcc tac tac tgt gag ggg gag tgt gcc ttc cct ctg aac tcc tac atg     1161
Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn Ser Tyr Met
                360                 365                 370

aac gcc acc aac cac gcc atc gtg cag acg ctg gtc cac ttc atc aac     1209
Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His Phe Ile Asn
                375                 380                 385

ccg gaa acg gtg ccc aag ccc tgc tgt gcg ccc acg cag ctc aat gcc     1257
Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln Leu Asn Ala
        390                 395                 400

atc tcc gtc ctc tac ttc gat gac agc tcc aac gtc atc ctg aag aaa     1305
Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile Leu Lys Lys
        405                 410                 415

tac aga aac atg gtg gtc cgg gcc tgt ggc tgc cac tagctcctcc         1351
Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His
420                 425                 430

gagaattcag accctttggg gccaagtttt tctggatcct ccattgctcg ccttggccag    1411

gaaccagcag accaactgcc ttttgtgaga ccttcccctc cctatcccca actttaaagg    1471

tgtgagagta ttaggaaaca tgagcagcat atggcttttg atcagttttt cagtggcagc    1531

atccaatgaa caagatccta caagctgtgc aggcaaaacc tagcaggaaa aaaaaacaac    1591
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gcataaagaa aaatggccgg gccaggtcat tggctgggaa gtctcagcca tgcacggact   1651

cgtttccaga ggtaattatg agcgcctacc agccaggcca cccagccgtg ggaggaaggg   1711

ggcgtggcaa ggggtgggca cattggtgtc tgtgcgaaag gaaaattgac ccggaagttc   1771

ctgtaataaa tgtcacaata aaacgaatga atgaaaaaaa aaaaaaaaaa a   1822

<210> 11
<211> 431
<212> PRT
<213> Homo sapiens

<400> 11

Met His Val Arg Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala
1   5   10   15

Leu Trp Ala Pro Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser
            20   25   30

Leu Asp Asn Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser
        35   40   45

Gln Glu Arg Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu
    50   55   60

Pro His Arg Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro
65   70   75   80

Met Phe Met Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Gly Gly
                85   90   95

Gly Pro Gly Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser
            100   105   110

Thr Gln Gly Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr
        115   120   125

Asp Ala Asp Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys
    130   135   140

Glu Phe Phe His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu
145   150   155   160

Ser Lys Ile Pro Glu Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile
                165   170   175

Page 19

```
Tyr Lys Asp Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Phe Arg Ile
            180             185                 190

Ser Val Tyr Gln Val Leu Gln Glu His Leu Gly Arg Glu Ser Asp Leu
            195             200                 205

Phe Leu Leu Asp Ser Arg Thr Leu Trp Ala Ser Glu Glu Gly Trp Leu
    210             215                 220

Val Phe Asp Ile Thr Ala Thr Ser Asn His Trp Val Val Asn Pro Arg
225             230                 235                 240

His Asn Leu Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser
                245                 250                 255

Ile Asn Pro Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn
            260             265                 270

Lys Gln Pro Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Phe
            275             280                 285

Arg Ser Ile Arg Ser Thr Gly Ser Lys Gln Arg Ser Gln Asn Arg Ser
    290             295                 300

Lys Thr Pro Lys Asn Gln Glu Ala Leu Arg Met Ala Asn Val Ala Glu
305             310                 315                 320

Asn Ser Ser Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr
                325                 330                 335

Val Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu
            340             345                 350

Gly Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn
            355             360                 365

Ser Tyr Met Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His
    370             375                 380

Phe Ile Asn Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln
385             390                 395                 400

Leu Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile
            405             410                 415
```

Page 20

```
Leu Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His
        420              425              430
```

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<210>  12
<211>  3151
<212>  DNA
<213>  Mus musculus

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aagcagagcg  cggggacggc  ggccgggagc  ggatcggagc  acgggacccg  cgccgggtc    180

tcgtgcgtcc  ctgcggatgg  gcgcgccgcc  gagccggcgc  taactgggat  cctcgctgga   240

acaggaggga  cagtattttc  tacctttcca  aaccgcagac  caagaagcta  aggagaatct   300

atgtaaatat  actgaaatct  ctgttggctc  tgcgcccaac  accccggagc  tggcacctca   360

ccctgtctga  ggagcgtgta  gaactagacc  agccgctatg  aatgtgacca  gcttgttttc   420

attcacaagt  ccagctgtga  agagactcct  tgggtggaaa  cagggcgatg  aagaagagaa   480

atgggcagag  aaagctgtgg  acgctttggt  gaagaaactg  aagaagaaga  aggggccat    540

ggaagagctg  agaaggccc   tgagctgccc  tggacagccg  agtaactgcg  tcaccattcc   600

tcgctccctg  gatggcaggt  tgcaggtgtc  ccaccggaag  ggactacctc  atgtcattta   660

ttgccgtgtg  tggcgctggc  ccgacctcca  gagccaccat  gaactgaagc  tctctggaatg   720

ctgtgagttc  ccatttggtt  ccaagcagaa  ggaggtctgc  atcaacccct  accactataa   780

gcgagtggag  agcccggttc  tcccgccggt  gctggttccg  aggcacagcg  agtacaatcc   840

tcagcacagc  cttctggctc  agttccgcaa  cctgggacaa  aatgagcctc  acatgccact   900

gaacgccacg  ttcccagact  ctttccagca  gcccaacagc  cacccgttcc  cccactcccc   960

caacagcagc  taccccaact  ctcctggcgg  cagcagcagc  acctaccctc  actccccaac  1020

cagctcagac  ccgggcagcc  cttttcagat  gccagctgac  acaccccccac  ctgcttacct  1080

gcctcctgaa  gaccccatgg  cccaggatgg  ctctcagccc  atggacacga  acatgatggc  1140

gcctccactg  cccgctgaaa  tcagcagagg  agatgttcag  gcagttgctt  acgaggaacc  1200

aaaacactgg  tgctctattg  tgtactatga  gctcaacaac  cgtgtgggtg  aagcgttcca  1260

cgcctcgtcc  accagcgtgc  tggtggatgg  tttcacagat  ccgtccaaca  ataagaaccg  1320

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acatattggg  aaaggagtcc  acctttatta  cgttggagga  gaggtgtatg  cggaatgcct  1440

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aatgtgcact attcggatga gcttcgtgaa gggttgggga ccgaatacc accggcagga    1680

tgttaccagc acccccctgct ggattgagat ccatctgcat ggccctctcc agtggctgga  1740

taaggttctg acccagatgg gctcaccccca caatcctatt tcatccgtgt cttaaaagac  1800

ctgtggcttc cgtctcttgc aaactatcga gccttgcatg tacttgaagg atggacaagt   1860

cagacaggat ggagacctga cgaaggagcc acgataatac ttgacctctg tgaccaacta   1920

ttggattgag aaactgacaa gccttggttg atagcaagaa ccctttcagt ttacattgtg   1980

acattctgtt gtaaaaatca actaaaatgc tgactttcag caggactttt gtgtatagtt   2040

aaaaaaaaaa gagatggcca agccagggac aaattatcta ttaggaaaaa agaaaaaaat   2100

gattgtaatc aatccttttg tgtggggtgt tggcagaagg ttggcgctga tagtctttct   2160

gaagtgggct ttcatcaggc tcagagccca cgttgaatca tcttctcatg ggttttctta   2220

atattttaaa actacttgtt tagaaatgaa tgggtttttt gtttgttttt aaagtacagg   2280

ttaatcgtta tgacatgcat agtaatcttt ctgaaactgt atgctggctg tattactgtc   2340

agaatgatgg caggcatatg ctctttgcta aatatgtata tacagaatat ttggaggtta   2400

tgaatagtct aaatggctag tgggtttaca gagtatctga ggggcggggt cgggaagaaa   2460

acgacggctg caaatgtaga ctataccgta aagctcagct tgctgcctta aacagacaag   2520

ctggtgtctg aatttgctgt gtttcagttt ttgtagagtt ttatctgact tctttttcttc   2580

tgtcttatcc gctccacggc acagttaagc agctggttaa ttcctctaac tgtgagagca   2640

gatgagtaat tccttctgtt cgcaaatcaa ctggcttcgt gtttcagtac ccagtatatg   2700

aaaagcttga attgaatgag cagttttat ggagtttaca gtacagacat aggctttgat    2760

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ggaaattttt aaataaaacc tgtcattatt gcttactttg attaaaaaaa aaaaaaaaaa   3060

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa   3120

aaaaaaaaaa aaaatttcat ctgtgtctta a                                  3151
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<210> 13
<211> 465

<212>   PRT
<213>   Mus musculus

<400>   13

Met Asn Val Thr Ser Leu Phe Ser Phe Thr Ser Pro Ala Val Lys Arg
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Leu Leu Gly Trp Lys Gln Gly Asp Glu Glu Glu Lys Trp Ala Glu Lys
                20   25   30

Ala Val Asp Ala Leu Val Lys Lys Leu Lys Lys Lys Lys Gly Ala Met
                35   40   45

Glu Glu Leu Glu Lys Ala Leu Ser Cys Pro Gly Gln Pro Ser Asn Cys
        50   55   60

Val Thr Ile Pro Arg Ser Leu Asp Gly Arg Leu Gln Val Ser His Arg
65   70   75   80

Lys Gly Leu Pro His Val Ile Tyr Cys Arg Val Trp Arg Trp Pro Asp
                85   90   95

Leu Gln Ser His His Glu Leu Lys Pro Leu Glu Cys Cys Glu Phe Pro
            100   105   110

Phe Gly Ser Lys Gln Lys Glu Val Cys Ile Asn Pro Tyr His Tyr Lys
            115   120   125

Arg Val Glu Ser Pro Val Leu Pro Pro Val Leu Val Pro Arg His Ser
    130   135   140

Glu Tyr Asn Pro Gln His Ser Leu Leu Ala Gln Phe Arg Asn Leu Gly
145   150   155   160

Gln Asn Glu Pro His Met Pro Leu Asn Ala Thr Phe Pro Asp Ser Phe
                165   170   175

Gln Gln Pro Asn Ser His Pro Phe Pro His Ser Pro Asn Ser Ser Tyr
            180   185   190

Pro Asn Ser Pro Gly Gly Ser Ser Ser Thr Tyr Pro His Ser Pro Thr
            195   200   205

Ser Ser Asp Pro Gly Ser Pro Phe Gln Met Pro Ala Asp Thr Pro Pro
    210   215   220

```
Pro Ala Tyr Leu Pro Pro Glu Asp Pro Met Ala Gln Asp Gly Ser Gln
225             230             235             240


Pro Met Asp Thr Asn Met Met Ala Pro Pro Leu Pro Ala Glu Ile Ser
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Arg Gly Asp Val Gln Ala Val Ala Tyr Glu Glu Pro Lys His Trp Cys
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Ser Ile Val Tyr Tyr Glu Leu Asn Asn Arg Val Gly Glu Ala Phe His
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Ala Ser Ser Thr Ser Val Leu Val Asp Gly Phe Thr Asp Pro Ser Asn
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Asn Lys Asn Arg Phe Cys Leu Gly Leu Leu Ser Asn Val Asn Arg Asn
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Ser Thr Ile Glu Asn Thr Arg Arg His Ile Gly Lys Gly Val His Leu
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Tyr Tyr Val Gly Gly Glu Val Tyr Ala Glu Cys Leu Ser Asp Ser Ser
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Ile Phe Val Gln Ser Arg Asn Cys Asn Tyr His His Gly Phe His Pro
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Thr Thr Val Cys Lys Ile Pro Ser Gly Cys Ser Leu Lys Ile Phe Asn
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Asn Gln Glu Phe Ala Gln Leu Leu Ala Gln Ser Val Asn His Gly Phe
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Glu Thr Val Tyr Glu Leu Thr Lys Met Cys Thr Ile Arg Met Ser Phe
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Val Lys Gly Trp Gly Ala Glu Tyr His Arg Gln Asp Val Thr Ser Thr
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Pro Cys Trp Ile Glu Ile His Leu His Gly Pro Leu Gln Trp Leu Asp
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Gln Asn Gly Gln Glu Glu Lys Trp Cys Glu Lys Ala Val Lys Ser Leu
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Val Lys Lys Leu Lys Lys Thr Gly Arg Leu Asp Glu Leu Glu Lys Ala
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Ile Thr Thr Gln Asn Cys Asn Thr Lys Cys Val Thr Ile Pro Ser Thr
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Cys Ser Glu Ile Trp Gly Leu Ser Thr Ala Asn Thr Val Asp Gln Trp
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Asp Thr Thr Gly Leu Tyr Ser Phe Ser Glu Gln Thr Arg Ser Leu Asp
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Gly Arg Leu Gln Val Ser His Arg Lys Gly Leu Pro His Val Ile Tyr
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Cys Arg Leu Trp Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys
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Ala Ile Glu Asn Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val
145                 150                 155                 160

Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro
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Pro Val Leu Val Pro Arg His Thr Glu Ile Leu Thr Glu Leu Pro Pro
             180                 185                 190

Leu Asp Asp Tyr Thr His Ser Ile Pro Glu Asn Thr Asn Phe Pro Ala
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Gly Ile Glu Pro Gln Ser Asn Tyr Ile Pro Glu Thr Pro Pro Pro Gly
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Tyr Ile Ser Glu Asp Gly Glu Thr Ser Asp Gln Gln Leu Asn Gln Ser
225                 230                 235                 240

Met Asp Thr Gly Ser Pro Ala Glu Leu Ser Pro Thr Thr Leu Ser Pro
             245                 250                 255

Val Asn His Ser Leu Asp Leu Gln Pro Val Thr Tyr Ser Glu Pro Ala
             260                 265                 270

Phe Trp Cys Ser Ile Ala Tyr Tyr Glu Leu Asn Gln Arg Val Gly Glu
             275                 280                 285

Thr Phe His Ala Ser Gln Pro Ser Leu Thr Val Asp Gly Phe Thr Asp
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Pro Ser Asn Ser Glu Arg Phe Cys Leu Gly Leu Leu Ser Asn Val Asn
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Arg Leu Tyr Tyr Ile Gly Gly Glu Val Phe Ala Glu Cys Leu Ser Asp
              340   345   350

Ser Ala Ile Phe Val Gln Ser Pro Asn Cys Asn Gln Arg Tyr Gly Trp
              355   360   365

His Pro Ala Thr Val Cys Lys Ile Pro Pro Gly Cys Asn Leu Lys Ile
    370   375   380

Phe Asn Asn Gln Glu Phe Ala Ala Leu Leu Ala Gln Ser Val Asn Gln
385   390   395   400

Gly Phe Glu Ala Val Tyr Gln Leu Thr Arg Met Cys Thr Ile Arg Met
              405   410   415

Ser Phe Val Lys Gly Trp Gly Ala Glu Tyr Arg Arg Gln Thr Val Thr
              420   425   430

Ser Thr Pro Cys Trp Ile Glu Leu His Leu Asn Gly Pro Leu Gln Trp
              435   440   445

Leu Asp Lys Val Leu Thr Gln Met Gly Ser Pro Ser Val Arg Cys Ser
    450   455   460

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Page 28

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Asp Glu Leu Glu Lys Ala Ile Thr Thr Gln Asn Val Asn Thr Lys Cys
    50                  55                  60


Ile Thr Ile Pro Arg Ser Leu Asp Gly Arg Leu Gln Val Ser His Arg
65                  70                  75                  80


Lys Gly Leu Pro His Val Ile Tyr Cys Arg Leu Trp Arg Trp Pro Asp
                85                  90                  95


Leu His Ser His His Glu Leu Arg Ala Met Glu Leu Cys Glu Phe Ala
            100                 105                 110


Phe Asn Met Lys Lys Asp Glu Val Cys Val Asn Pro Tyr His Tyr Gln
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Pro Glu Thr Pro Pro Pro Gly Tyr Leu Ser Glu Asp Gly Glu Thr Ser
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Pro Asn Pro Met Ser Pro Ala His Asn Asn Leu Asp Leu Gln Pro Val
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            245             250             255

Val Asp Gly Phe Thr Asp Pro Ser Asn Ser Glu Arg Phe Cys Leu Gly
        260             265             270

Leu Leu Ser Asn Val Asn Arg Asn Ala Ala Val Glu Leu Thr Arg Arg
        275             280             285

His Ile Gly Arg Gly Val Arg Leu Tyr Tyr Ile Gly Gly Glu Val Phe
    290             295             300

Ala Glu Cys Leu Ser Asp Ser Ala Ile Phe Val Gln Ser Pro Asn Cys
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Page 35

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Ala Val Ser Ile Phe Tyr Asp Leu Pro Gln Gly Ser Gly Phe Cys Leu
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Page 47

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Page 48

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Page 53

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Arg Phe Cys Leu Gly Leu Leu Ser Asn Val Asn Arg Asn Ser Thr Ile
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Cys Lys Ile Pro Ser Gly Cys Ser Leu Lys Val Phe Asn Asn Gln Leu
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INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7   A61K38/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7   A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TAMAKI ET AL: "Intracellular signaling of osteogenic protein-1 through Smad5 activation" JOURNAL OF CELLULAR PHYSIOLOGY, vol. 177, 1998, pages 355-363, XP008048090 * See page 355 (Abstract) *	1-5,7-49
Y	AOKI ET AL: "Synergistic effects of different bone morphogenetic protein type I receptors on alkaline phosphatase induction" JOURNAL OF CELL SCIENCE, vol. 114, 2001, pages 1483-1489, XP002302367 * See pages 1483-1484 (Abstract and Introduction, esp. last sentence), figures 1-5, and pages 1487-1488 (Discussion) *	1-5,7-49

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| X | Further documents are listed in the continuation of box C. | | X | Patent family members are listed in annex. |

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 2005	17/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Korsner, S-E

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	YEH ET AL: "Osteogenic protein-1 (OP-1, BMP-7) induces osteoblastic cell differentiation of the pluripotent mesenchymal cell line C2C12" JOURNAL OF CELLULAR BIOCHEMISTRY, vol. 87, 2002, pages 292-304, XP002302368 * See pages 300-303 (Discussion) *	1-5,7-49
Y	FORSLUND ET AL: "A comparative dose-response study of cartilage-derived morphogenetic protein (CDMP)-1, -2 and -3 for tendon healing in rats" JOURNAL OF ORTHOPAEDIC RESEARCH, vol. 21, 2003, pages 617-621, XP002330748 * See pages 617-618 (Introduction), and pages 619-621 (Discussion) *	1-5,7-49
Y	TAKASE ET AL: "Induction of Smad6 mRNA by bone morphogenetic proteins" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 244, 1998, pages 26-29, XP002219536 * See page 26 (Abstract) *	1-5,7-49
Y	MACÍAS-SILVA ET AL: "Specific activation of Smad1 signaling pathways by the BMP7 type I receptor, ALK2" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, 1998, pages 25628-25636, XP002330481 * See page 25630 (right column) - page 25631 (left column) *	1-5,7-49
Y	NISHIDA ET AL: "Osteogenic protein 1 stimulates cell-associated matrix assembly by normal human articular chondrocytes" ARTHRITIS & RHEUMATISM, vol. 43, 2000, pages 206-214, XP002330479 * See pages 206-207 (Introduction) *	1-5,7-49
Y	SIMANK ET AL: "Das Wachstumsfaktorkomposit aus GDF-5 und mineralisiertem Kollagen verbessert die Ausheilung einer Hüftkopfnekrose" ORTHOPÄDE, vol. 33, January 2004 (2004-01), pages 68-75, XP002330749 * See page 71 (English summary) *	1-5,7-49
Y	US 6 531 445 B1 (COHEN ET AL) 11 March 2003 (2003-03-11) * See columns 2-3 (tissues) and 6-7 (proteins useful) *	1-5,7-49

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/059932 A (YISSUM RESEARCH DEV. COMP. OF THE HEBREW UNIV. / GBF-GESELLSCHAFT) 24 July 2003 (2003-07-24) * See page 1 (Field of the invention), pages 11 and 21 *	1-5,7-49
P,X	YEH ET AL: "Cartilage-derived morphogenetic proteins enhance the osteogenic protein-1-induced osteoblastic cell differention of C2C12 cells" JOURNAL OF CELLULAR PHYSIOLOGY, vol. 201, December 2004 (2004-12), pages 401-408, XP008048134 * See page 401 (Abstract) *	1-5,7-49

INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

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   Although Claims 1-49 (partially) are directed
   to a method of treatment of the human body,
   the search has been carried out and based
   on the alleged effects of the compounds.
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2. [ ] Claims Nos.:
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)

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